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Early Detection of Alzheimer Disease using Brain Connectome: A Brief Survey

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Abstract - *Alzheimer disease is one of the most common neurodegenerative disorder/disease. People are now aware about this disease, due to different technologies available to detect it at an early stage. Around 7.15 million people are predicted to be affected by Alzheimer's by the end of 2030 globally [1]. It is observed that elderly people are more prone to suffer from Alzheimer's or any other neurodegenerative disorder. Alzheimer's is incurable; once a person is affected he/she has to live with it lifelong as it is generally detected during the later stages. Early detection of Alzheimer's primarily helps in delaying its progression, improvising the living of people suffering from the disease. Secondarily, it gives a better view and in-depth knowledge to doctors and researchers in understanding and treating the disease. Hence, an overview of some of the recent techniques for early detection of Alzheimer's is presented in this paper. Some of the factors that help in diagnosing the disease in its early stages are: Brain connectomes, Cerebrospinal fluids (CSF) and amyloid levels (p-tau or t-tau), age of the patient, etc. In one of the methods, CSF levels, p-tau levels and age are the prime factors used for detecting Alzheimer's. Second method detects the disease using structural and functional connectomes. Brain morphometry and structural connectomes are used with different machine learning algorithms in the third technique. In the next method, prion-like mechanism is simulated for better understanding of the disease. Structural and functional connectomes of the subjects are evaluated using graphical methods in the last technique.*

***Key Words*: Alzheimer's Disease (AD), Cerebrospinal Fluid (CSF), Connectome, Human Connectome Project(HCP), Mild Cognitive Impairment (MCI), MRI, Neurodegenerative Disorder.**

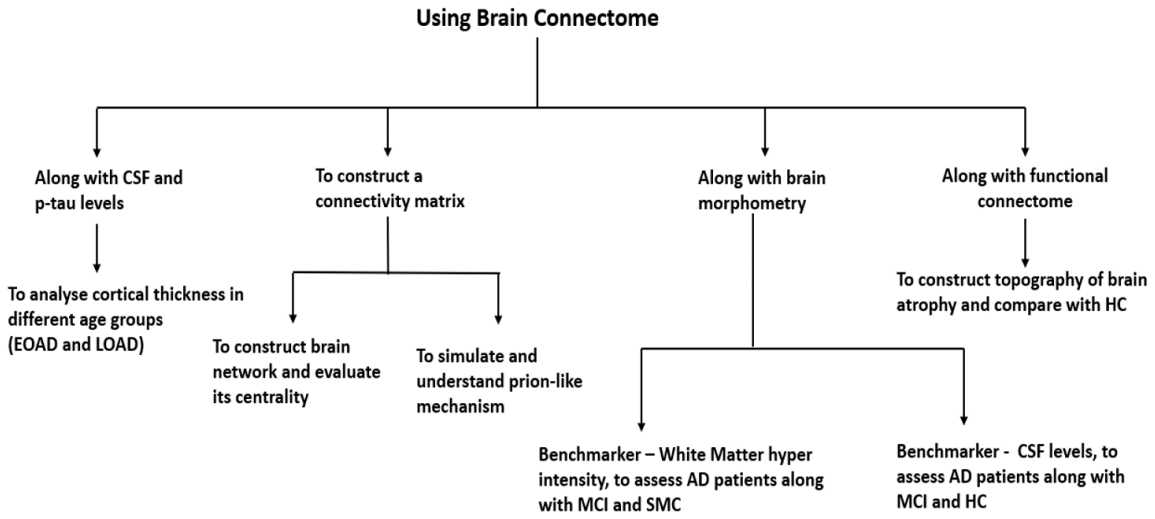
1. INTRODUCTION

Alzheimer's Disease (AD) is a neurodegenerative disorder that leads to atrophy in the brain. People suffering from Mild Cognitive Impairment (MCI) are those who have issues with their memory. In most of the cases, there is a probability that patients with MCI are further diagnosed with AD or dementia. Amnestic MCI which is a subtype of MCI, is discussed in the subsequent sections. Symptoms of AD are memory loss, difficulty in problem-solving and familiar task-completion, trouble in visualizing images and objects around them, etc.

Connectome is a complete representation of structural connectivity of nervous system of an organism. Connectometics is an area of science which deals with mapping, assembling and analyzing data on neuron connectivity. To gain better knowledge about structural and functional connectivity within robust human brain, and to produce data that will ease the research into brain disorders like Dyslexia, Autism, Alzheimer's and Schizophrenia; NIH (National Institute of Health) came up with a project called Human Connectome Project (HCP) in the year 2009.

In this paper, brain connectomes of the subjects are primarily used in early detection of AD. Fig-1 gives an overview of various techniques discussed in this paper: (1) CSF and p-tau levels of the patients of different ages are considered and the influence of age on AD is discussed. (2) Subjects are evaluated based on their amyloid pathology in the brain connectomes along with other neurodegenerative signs for early detection. (3) Using brain morphometry along with connectome, AD is detected using two different benchmarks - White matter hyper intensity and CSF levels. (4) Prion-like mechanism in AD is simulated using different models. Better understanding of this mechanism can delay the progression of the disease. (5) Different graphical methods are used to evaluate the functional and structural connectomes of AD patients. These subjects are then compared with Healthy Controls (HC) at different stages of the disease.

Fig-1: A hierarchical representation of the techniques.



2. ORGANIZATION OF THE PAPER

The paper is organized as follows: A brief overview of Alzheimer's Disease and connectome is provided in Section I. Literature Survey is presented in Section III. Section IV discusses brain connectome and various parameters used to detect Alzheimer's. Section V presents results of all the methods. Discussion is provided in Section VI followed by conclusion in Section VII.

3. LITERATURE SURVEY

AD is a major challenge faced by people all over the world. Ageing is a crucial factor contributing to diseases like Alzheimer's, Dementia, Parkinson's, etc. According to the Alzheimer's Association [2], approximately 81% of people suffering from Alzheimer's belong to the Late Onset AD (LOAD) group. Records state that between the years 2000 and 2013, there has been an increase in death by 71% due to this disease [2].

High Alzheimer's rates have been seen in countries like United States, Switzerland, Canada, Finland, Sweden, Iceland, etc. Scientists are currently working on different factors responsible for the cause of AD, such as lifestyle, environmental-factors, genetics, etc. According to a survey, it is seen that women are more likely to suffer from Alzheimer's when compared to men [3]. Researches at University of Cambridge, show that the disease is caused due to smoking, lack of exercise, depression, illiteracy, etc. [4]. In India, a tiny fraction of people who suffer from Alzheimer's are clinically treated. By the end of the year 2030, it is predicted that the rate of AD can reach up to 7.5 million people.

4. AD DETECTION TECHNIQUES

In this section, we provide a survey on the different techniques used for early detection of AD:

4.1 Using CSF and p-tau levels

In [5], subjects are taken from the AD Neuroimaging Initiative (ADNI) [6] database for the study. The main aim of this database, is to check whether MRI (Magnetic Resonance Imaging), PET (Positron Emission Tomography) or any other neuropsychological method can be used to assess the progression of MCI or to detect the early stage of AD. The individuals were chosen based on their CSF and p-tau levels and also on another important factor, age [5]. Individuals are classified as Early Onset AD (EOAD) if their age is less than 65 years, Late Onset AD (LOAD) if their age is greater than 80 years and subjects with Alzheimer's at the age of 80. A 1.5T or 3T scanner is used for collecting the MRI scans of the subjects, with MPRAGE being the standard protocol and having the following parameters: Repetition Time (TR), Echo Time (TE), Interaction Time (TI), etc. The two tests performed for analysis are: Rey Auditory Verbal Learning Test (AVLT) and Boston Naming Test (BNT). For the ADNI cohort, the BNT test was given where the subjects were asked to identify 30 black and white lines drawn for an object. A Z-score was given for each subject based on their performance in the tests, their CSF – amyloid levels and their age [5]. From the reconstructed brain of each subject, cortical thickness metrics were mapped to the inflated surfaces [13], which were later mapped to the FreeSurfer templates (fsaverage). In this model, the cortical thickness present in the ROI (Region of Interest) was taken as the independent variable and the cortical thickness of the remaining areas were taken as dependant variables. In addition, chi-square test or an analysis on covariance was

also performed as part of statistical analyses. IBM SPSS 21.0 was used to perform the statistical analyses in the study [5].

4.2 Using CSF levels and Neurodegenerative disorder signs

The subjects for [7] were taken from a Swedish Bio FINDER study [8], whose main aim was to detect early stages of AD, examine them and to evaluate other neurodegenerative disorders. These subjects were assessed from the year 2010 to 2016. They followed a standard protocol where different tests were performed: MMSE (Mini Mental State Examination), the 10-word list delay recall test and a test for cognitive speed (AQT) [9] and other such neurological and psychiatric assessments. In this study, subjects were classified based on their amyloid and neurodegenerative biomarkers into different categories as: (1) Subjects with normal CSF levels and normal AD neurodegenerative signs (A-N-), (2) Subjects with abnormal CSF levels but normal AD neurodegenerative signs (A+N-), (3) Subjects with normal CSF levels but abnormal AD neurodegenerative signs (A-N+), (4) Subjects with abnormal CSF levels and abnormal AD neurodegenerative signs (A+N+) [10]. The neurodegenerative signs of the subjects were computed using 2 different neuro-anatomical biomarkers. One of the biomarkers consisted of the following regions: entorhinal [11], inferior-temporal, middle-temporal and fusiform having an average amount of cortical thickness [12-15]. The other biomarker consisting of an average amount of hippocampal volume was adjusted by the intracranial volume. These two biomarkers were provided by FreeSurfer (version 6.0) [16]. Subjects were analyzed based on their CSF levels at the same center [17]. The MRI images of all the subjects were acquired at the Skane University Hospital, Sweden. Based on the protocol, two types of scans were taken 1) A diffusion weighted scan and 2) A T1 weighted scan [7]. These scans had their respective parameters in terms of repetition time (TR), echo time (TE), voxel size, matrix size, slice thickness, etc. A tract graphical map was constructed using their MRI scans, to visualize and analyze their structural connectivity among different regions of the brain [7]. These maps show the cortical and sub-cortical fibers [18] from which a weighted connectivity matrix was obtained which is later converted into a binary matrix using different intensities to easily construct a brain graph. A total of 82 regions (nodes) were formed in the graph, out of which 62 are cortical and 14 are sub-cortical regions [7], there-by providing an 82x82 matrix where the edges of the graph represent white matter fibers. Different graph theory methods have been used to analyze this graph. Ability of a network for specialized processing within dense interconnected groups of regions defines its segregation. Clustering coefficient [19] and modularity [20] of a network come under segregation. Relative importance of the nodes in the network define the centrality of the network. Non-parametric permutation tests [21] were performed to assess the difference between groups in the graph. A network based approach was also used to identify specific regions within the network, that show abnormal structural connectivity.

4.3 Using different benchmarks

In [22], the data was taken from 211 seniors from the National Health Insurance Service Ilsan Hospital (NHIS-IH), which is in Goyang, South Korea. These patients were treated from the year 2010 to 2015. The patients were diagnosed based on AD as well as Peterson's MCI criteria. In the diagnosis of MCI, individuals were tested based on their neuropsychological score [22]. For the diagnosis of AD, patients with a small vessel disease were marked as "AD with small vessel disease". From the sample data, patients were classified as: 110 patients with AD, 64 with MCI and 37 patients with SMC (Subjective Memory Complaints) [22]. Different multimodal MRIs, such as, T1-MPRAGE TE MRI, T2-FLAIR MRI, Diffusion MRI, T1 weighted anatomical MRI were acquired. All these MRI scans were taken with different matrix parameters, voxel sizes and some with or without diffusion weighting. MRI analysis was done based on structural and diffusion MRIs. Structural connectomes were estimated using both these MRIs. Approximately 33,698 features were obtained from the connectomes constructed per subject [23-25]. Three multimodal phenotypes [26-28], namely: (I) Logistic Regression with L1 and L2 regularization, (II) Random forest and (III) Support Vector Machine (SVM) with a linear kernel model were used. In previous studies, an extensive use of binary classification is made [28]. Hence, binary classification is chosen for a better comparison. Six different 1-vs-1 binary classifications were made: AD vs SMC, AD vs MCI, MCI vs SMC, AD (only) vs AD with small vessel disease, AD (only) vs MCI and AD (only) vs SMC. A python library, scikit-learn [26] which is used for Machine Learning (ML) is used for all these analyses. Existing biomarkers are used as benchmark models. From T2-FLAIR images white matter intensity measures were estimated. For this a supervised ML algorithm was used. Secondly, CSF biomarkers were used from the ADNI-2 cohort. This biomarker is used for diagnosis of AD, MCI and the progression to AD from MCI [29-30].

4.4 Using Prion-like mechanism

One of the key characteristics to understand the brain is by considering it as an organized network, at both the physical and functional levels [31-32]. Here, the different parameters that are considered in the prion-like paradigm of AD are evaluated. For this, 418 subjects from the Human Connectome Project were taken and their weighted connectivity graphs were evaluated. The main aim being to model the tau proteins, is achieved by using a simple kinetic model. In this model [31], the focus is on two types of protein configurations - the natural healthy ones and the misfolded ones. At two different rates, the misfolded proteins recruit the healthy ones and healthy proteins bind to the misfolded ones and adopt their conformations. The spreading of healthy and misfolded proteins in the brain's

connectome, which is represented as a graph is modelled as a diffusion across it. The original graph with 1015 nodes and 37,477 edges is mapped onto a graph with 83 nodes and 1130 edges. In short, it is summarized as follows: the connectivity of the graph is represented with a diagonal matrix, D_{ii}, which shows the degree of each node *i*. The adjacency matrix A_{ij} of the graph, shows the ratio of mean fiber number to mean fiber length for each node. The small-scale model of human brain can be clearly illustrated with the help of the adjacency matrix, across different regions of the brain. The different parameters used to simulate the brain network model are also explained in [31]. A biomarker curve defines how well a body can respond to a treatment or condition. It would take nearly 30 years of time to observe the results in a model, but a matter of seconds in a laptop or computer. Another parameter is the Infection Times. For this parameter, the tau proteins were seeded into 83 different regions of the brain, and then their individual infection times as biomarker curves were computed. A better understanding of prion-like mechanisms can help us block the misfolding of proteins, thereby making advancements in protein clearance using different antibodies and smaller molecules. Reduction in misfolds and increasing the clearance are two therapeutic strategies that are proven to delay or prevent the progression of the disease.

4.5 Using Amnestic MCI signs

In [33], Department of Neurology, Scientific Institute and University Vita Salute had selected people with AD and mild amnestic MCI. Three years later, 53% amnestic MCI patients were diagnosed with AD. This was based on several factors of the individuals such as age, gender, disease duration (in years), education (in years), ADL (Activities of Daily Living), IADL (Instrumental Activities of Daily Living), etc. The assessment was performed based on the MRI results of the patients only. There were different tests taken to evaluate them: MMSE (Mini Mental State Examination), Rey Auditory Verbal Learning Test (AVLT), long-term and short-term memory with verbal memory prose, attentive and executive functions with attentive matrices, the clock drawing test, the phonemic and semantic fluency tests and language with token test, etc. The same procedure was followed for all the 88 healthy patients (Healthy Control) [33], so as to use it as reference for comparison. There are mainly two aims in this study [33]: (1) To observe the functional and structural connectomes of AD and amnestic MCI patients. Grey Matter parcellation was performed based on 220 similarly sized brain regions (including the cerebral cortex and ganglia excluding cerebellum). Different metrics such as nodal strength, path length, clustering and modularity to assess the global networks of the patients were used. (2) To assess and infer the relation between HC brain network architecture and topography of brain atrophy in patients. The point at which maximum atrophy occurs, is said to be the epicentric region for AD, c-amnestic MCI, nc-amnestic MCI patients.

5. RESULTS

Results obtained based on the different techniques used and tests performed on the subjects in various phases of AD, are presented below:

As a result of technique used in [5], it is observed that the LOAD group has a higher percentage of female patients, and a little lower rate of Apolipoprotein E (APOE) carriers when compared to the EOAD group. There were 49 subjects which were considered under the LOAD group and 26 subjects under the EOAD group. The main difference between the two groups of subjects is in the "spatial topography of atrophy". In case of EOAD group, the atrophy was observed to be mostly evident in the inferior parietal lobule, lateral temporal cortex, Posterior Cingulate Cortex (PCC) and precuneus regions of the brain. For LOAD group, atrophy was mostly observed in the anterior MTL and anterior temporal cortex, along with higher prominence in the caudal ventral and lateral temporal cortex regions of the brain. It is observed that the PCC or the procuneus region of the brain is the "epicenter" for atrophy in case of EOAD group of subjects, whereas for the LOAD group of subjects the "epicenter" of atrophy lies in the anterior MTL region of the brain. When the structural covariance maps of the two groups EOAD (epicenter at PCC) and LOAD (epicenter at anterior MTL) were overlapped for comparison, it was observed that these two are independent of each other.

In total, 357 individuals participated for the study in [7] with 171 subjects in the CN A-N- category, 43 subjects in the CN A+N- category, 86 subjects in the CN A-N+ category and 57 subjects in the CN A+N+ category. Seven different groups were formed (4 categories individually, the rest 3 used for comparison with one another). Mean or standard deviation was computed for each individual category and Chi-Square test was performed for comparison groups. The mean path length had significantly increased in CN A-N+ and A+N+ individuals when compared to CN A-N-. There was significant decrease in global efficiency of CN A+N- individuals at network densities with respect to CN A-N- individuals. There were no significant differences in mean clustering or modularity of CN A+N- with respect to CN A-N- individuals. There were significant differences in terms of nodal degree for CN A-N+ individuals with respect to CN A-N- individuals. The number of connections also have remarkable differences for CN A+N+ individuals with respect to CN A-N-, but there were no variations in CN A+N- individuals with respect to CN A+N+. An abnormal decrease in structural connectivity is seen among regions of the brain in CN A-N+ and CN A+N+ individuals when compared to CN A-N- individuals. Using the modular architecture for CN A-N- individuals as reference, different regions of the brain were coloured. Different areas of the brain were taken into consideration for comparison between the groups. A subset of the cohort was scanned again after 2 years and was compared on different metrics such as global efficiency, path length, modularity, etc.

Different accuracies were shown in the NHIS-IH cohort [3], based on different parameters used such as Morphometry and Structural connectome, Morphometry only, Structural connectome only and using a White Matter intensity as a Benchmark model. They were used on different classifiers such as AD vs SMC, SMC vs MCI and AD vs MCI. Another set of accuracies were shown for the ADNI-2 cohort, using CSF biomarkers as benchmark models, Morphometric features and Structural connectomes individually, and in a combined form for comparison. From the NHIS-IH cohort, higher accuracies (0.99 for AD vs SMC) were seen in the different categories when connectome alone of the subjects was considered. In the ADNI -2 cohort, higher accuracies (0.97 for AD vs SMC) were observed in different categories that implemented brain morphometry or connectome of the subjects.

There are two strategies discussed in [31]: the first strategy, suggests that even a small amount of reduction in the misfolds of the proteins in the early stage of Alzheimer's, can delay the progression by several decades. The second strategy, provides a mechanism to increase the clearance rate, which also thereby reduces misfolds and delays the development of the disease by several decades. The initial observations were made, using the biomarker curve, which is the entorhinal region of the brain. Entorhinal region is the second highest in terms of infection time. This could explain at-least one reason, why it is difficult to diagnose tau proteins during early stages of AD. The brain network model accurately predicts the spreading of tau-proteins in the brain network. The potential of the model is simulated through "biomarker curves, infection times and therapeutic intervention". A better understanding of prion-like mechanisms can help us block the misfolding of proteins, thereby making advancements in protein clearance using different antibodies and smaller molecules. Different methods of graph theory were used for better understanding of the brain functions. The main aim of this study, was to combine network diffusion and model the prion-like mechanism of tau proteins in the brain connectome to efficiently observe the key features of pathogenic proteins in AD.

There were severe abnormalities in the functional and structural connectomes of AD patients [33], when compared to Healthy Control (HC). Higher percentage of widespread alterations in the structural connectivity in terms of decreased FA (Fractional Anisotropy) along with increased MD (Mean Diffusivity) were seen in AD patients when compared to the HC. The c-amnestic MCI represent patients who convert to AD from MCI and the nc-amnestic MCI represent the non-converters. The c-amnestic MCI patients have shown lower global network metrics in terms of nodal degree, global efficiency and clustering coefficient in comparison to the HC. For lobar networks, c-amnestic MCI graphs have shown lower nodal degree and local efficiency in the temporal and parietal lobes. For nc-amnestic MCI patients, alterations were not seen in the global networks. In case of lobular graphs, there was only lower clustering coefficient in the parietal lobe region relative to HC. There were not much differences seen in the AD and c-amnestic MCI patients, in the global and lobular networks. There were abnormalities seen in AD patients graph relative to the nc-amnestic MCI patients.

6. DISCUSSION

A comparison chart is shown in table 1, which depicts the different objectives behind the papers, their implementations, observations made and the results that were obtained, respectively. Each one of the approaches discussed here, mainly aims at detecting Alzheimer's at an early stage (preclinical phase). In [5], age and its influence on Alzheimer's are taken. Along with age, brain connectome and CSF levels of the subjects are also taken for analysis. In [7], the disease is detected using neurodegenerative signs and mechanism of AD of the subjects. The subjects are classified, compared with HC and some conclusions are drawn, based on these comparisons. In study [3], subjects are diagnosed for AD based on their MCI criteria and three different ML algorithms are applied on the data collected from the subjects. The subjects are analysed based on their brain morphometry and structural connectome. Prion-like mechanism which is seen in subjects suffering from AD is simulated in [31]. This mechanism depicts the spreading of tau proteins within the subject's brain. The simulation was performed using a kinetic model, which was modelled into a graph and evaluated based on different parameters such as infection times, biomarker curves and therapeutic strategies. A better understanding of this mechanism, can help in reducing the spreading of tau proteins. This in turn, reduces the progression of the disease by almost a decade. The structural and functional connectomes of AD and amnestic MCI patients are considered for this study in [33]. Here the network architecture is compared with HC group. A number of factors are considered, such as age, gender, ADL (Activities of Daily Living) and IADL (Instrumental Activities of Daily Living) for comparison.

Table 1: A Comparison Chart

Factors	Age factor [5]	CSF levels and Neurodegenerative Disorder [7]	Different benchmarks [22]	Prion-like mechanism [31]	Amnestic MCI [33]
(1)	Early detection of AD using CSF and p-tau levels.	Detect early mechanisms of AD and estimate their Neurodegenerative disorder.	Subjects from 2 different cohorts were taken for diagnosis of AD based on MCI criteria.	Evaluation of prion-like mechanism in AD. To model the tau proteins in the brain using a simple kinetic model.	This study mainly focuses on functional and structural connectome of AD and amnestic MCI patients, and also to compare network architecture of healthy controls against different patients.
(2)	Classifying the subjects based on their age into 2 groups-EOAD and LOAD.	Subjects were classified into 4 categories based on their CSF levels and Neurodegenerative disorder signs-A+N+, A+N-, A-N+ and A-N-.	Subjects from the sample data were categorized as 110 with AD, 64 with MCI and 37 with SMC.	From "The Human Connectome Project", 418 subjects were taken for this study. And for each subject its weighted connectivity graph was evaluated.	People suffering from AD and amnestic MCI were taken from the Department of Neurology, Scientific Institute and University Vita Salute, San Raffaele, Milan.
(3)	Subjects were given tests, based on their performance and biomarker levels they were then given a Z-score.	CSF samples of all subjects were collected and analyzed, whereas their neurodegenerative signs were tested using 2 biomarkers.	Implementation of 3 different ML algorithms (Logistic Regression L1 and L2, Random Forest and SVM) on different multimodal phenotypes of the subjects.	The prion-like mechanism, is modelled into a graph across the brain connectome and then evaluated based on different parameters such as infection times, therapeutic intervention and biomarker curves.	Based on different factors such as age, gender, disease duration (in years), ADL (activities of daily living), IADL (instrumental activities of daily living), comparison was done.
(4)	**Results:** Statistical Analysis on the epicenter (region chosen in the brain based on the cortical thickness).	**Results:** Seven groups were formed which were compared with one another based on different factors such as mean path length, global efficiency, clustering and modularity, by computing mean (or standard deviation).	**Results:** NHIS-IH cohort was analyzed using 2 parameters- Brain Morphometry and Structural Connectome.	**Results:** Main aim of this study is to model and observe the role of tau proteins in the prion-like mechanism in AD, efficiently.	**Results:** Patients with AD and amnestic MCI, were compared with Healthy Controls. AD patients showed decreased FA and increased MD, whereas amnestic MCI patients were classified as c-amnestic MCI and nc-amnestic MCI.

7. CONCLUSION

An effort has been made to analyze the different techniques used to detect AD through this paper. In the diagnosis of AD, it is observed that the patients are classified into different categories based on the factors mentioned in Table I. Each one of the techniques mentioned in this paper has its own approach to predict the disease. Among these, the technique which uses brain morphometry and connectomes of the patients has shown better results in terms of accuracy. The HCP has been collecting data of higher quality for HC so as to compare with AD patients. An initiative was taken by HCP in the year 2016 which is called as "Alzheimer's Disease Connectome Project (ADCP)". This project helps in understanding the disease at different stages during its development. Here amyloid and tau pathologies of the subjects are studied so as to predict the changes in their brain connectomes. As a future work, the brain connectomes of the subjects can be implemented along with advanced algorithms (Artificial Intelligence, ML, Deep Learning) to predict the disease in its preclinical phase.

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