Predictive Indicator from Alzheimer's disease

Interactive Qualifying Project

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APPENDIX

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Introduction:

Alzheimer's disease has become the biggest medical challenge in modern neurology, due to its prevalence and socio-economic burdens. The diseases have affected millions of people, and the number is expected to rise. Alzheimer's disease can lead to decrease in cognitive ability, memory loss, and daily functioning impairment. Therefore, it is important to have a proper method for early diagnosis and timely intervention for AD.

In recent years, Predictive Modeling and Pattern Recognition have become more popular in neuroscience that allows researchers to analyze early symptoms of diseases. This method can be very helpful in providing a snapshot of patents at baseline and tracking changes over time that signal the progression of Alzheimer's diseases. These predictive cognitive and functional assessments from the pattern can also lead to more evidence to understand the disease and provide better intervention and treatments. This study aims to utilize datasets that focus on baseline measurements and changes over time in cognitive and functional assessments among patients to predict outcomes related to Alzheimer's disease using publicly available datasets. The goal is to use the cognitive and functional score to find the correlation with the progression of Alzheimer's disease over time. Another important approach to analyze the early symptoms of Alzheimer's disease is the incorporation of MRI, which provides a detailed view of the brain structure and functionality. MRI scans are invaluable for capturing the baseline snapshot of patient's brain health and for monitoring anatomical changes over time, such as the progression of the brain atrophy associated with Alzheimer's disease. MRI images can reveal the brain structure changes pattern, which combining with the cognitive score analysis, can improve the predictive models, which used to forecast the development of Alzheimer's diseases. This approach can provide deeper insights into the disease and provide important information for

treatment. We hope to contribute a broader understanding of how early detection and continuous monitoring influence treatment strategies and patient care.

History of Alzheimer's diseases:

Dr. Alois Alzheimer's, a German Psychiatrist and neuropathologist describes the case of Auguste Deter, a patient that was diagnosed with memory loss, disorientation, and psychological changes. After Auguste's death, Dr's Alzheimer performed a brain autopsy and observed pathological features such as abnormal clumps and tangled bundles of fibers.

These abnormalities were what Alzheimer called "presenile dementia," which was renamed Alzheimer's diseases. Until the 20th century, researchers recognized Alzheimer's as the most common cause of dementia and that it was not limited to those under 65.

As the population increases, Alzheimer's diseases prevalence increased, causing more attention from the community. Alzheimer's disease was recognized as the most common cause of dementia and posed a major public health challenge, which lead to the establishment of organizations like the Alzheimer's Association in the United States, which was founded in 1980 to improve research and provide support to the AD patients.

To study the brain structure of Alzheimer, neuroimaging techniques such as CT scans and later MRI and PET scan are utilized. These techniques will allow better study of the brain and the changes that occur with Alzheimer's patients. The cognitive test development and rating scales helps to analyses and understanding the progression of the diseases.

How Alzheimer's disease is diagnosed:

Alzheimer's disease is diagnosed through a complete clinical assessment, which includes examining medical history, physical examination, neurological assessments, and cognitive testing to test memory impairment and other cognitive functions. Doctors or physicians can use different tools and tests, which includes Mini-Mental State Examination (MMSE) and Montreal

Cognitive Assessment (MoCA) to screen for cognitive decline and differentiate Alzheimer's from other forms of dementia. Neuroimaging techniques, such as magnetic resource imaging (MRI) or PET scans are utilized to observe changes in structural and functional in the brain that indicate Alzheimer's symptoms. Additionally, blood tests are utilized to rule out other conditions that are similar or contribute to cognitive symptoms, such as vitamin deficiencies. These combinations of evaluations allow physicians or healthcare professionals to diagnose with a high degree of certainty.

Executive Summary:

The goal of diagnosing Alzheimer's disease lies in the ability to provide detailed images of the brain’s structure, which allows physician to detect and assess change related to the Alzheimer's progression. MRI scans are important in identifying brain shrinkage or atrophy, which happens in the hippocampus and different regions important for memory and cognition. MRI scan can help monitor the disease’s progression and differentiate Alzheimer’s from other types of dementia based on the patterns of the brain atrophy. The use of MRI in diagnosing Alzheimer’s aims to improve the accuracy of the diagnosis, providing information for treatment decisions.

Objective: The primary goal of research is to understand the progression patterns of Alzheimer's Disease and identify factors that influence the rate of cognitive decline among patients. By understanding the dataset of participants, we hope to derive insights that could inform critical practices and therapeutic strategies. Additionally, we also utilize MRI in Alzheimer to understand the structural and functional changes occurring in the brain, which contributes to the development of Alzheimer's disease. By identifying small changes in the brain volume and structure before symptoms become apparent, MRI scans can help identify individuals at risk of developing Alzheimer's, which enables earlier intervention and monitoring. MRI imaging can also reveal the rate and pattern of brain atrophy, which provides insight into how quickly the diseases is advancing and helping clinician adjusting treatment plans.

Data and Methods. The dataset is derived from extensive Alzheimer's study, which includes demographic information, cognitive assessment scores, and diagnostic confidence levels. We have applied data preprocessing to make sure of the data quality and integrity. We also performed statistical methods such as correlation analysis and regression models to examine the relationships between various factors and AD progression. The dataset also includes the high-resolution MRI scan derived from Alzheimer's research.

Method:

The main goal of this study is to investigate how baseline cognitive and functional scores correlate with the progression of Alzheimer's diseases over time. We also need to make sure that our data consists of patients from diverse range of backgrounds with different stage of Alzheimer's disease such as preclinical stage and advanced stage. We begin by selecting individuals that are diagnosed with Alzheimer's disease or mild cognitive impairment that consists of baseline cognitive and functional assessment score. We also define independent variables to be baseline measures, which includes Mini-Mental State Examination (MMSE) score, Functional Activities Questionnaire (FAQ) scores, and Clinical Dementia rating (CDR) scores, with others available in the dataset. We defined our longitudinal data through metrics like Cognitive Tests, Functional Assessments, Behavioral and Psychological Symptoms, and Clinical Staging. By analyzing changes in these assessments over time, we can quantify the progression of Alzheimer's disease for an individual or within a cohort. We will perform statistical analyses using baseline scores, which serves as reference point to which future score are compared. They are crucial for identifying early cognitive and functional states of patients and for measuring the change or progression from these initial states. For example, a patient's baseline MMSE score may be 29 out of 30, indicating good cognitive function at the start of the study. However, after one year, the patient's MMSE scores drop to 23, which shows that there has been a cognitive decline. The analysis will also include subgroup analyses to explore how correlations differ across various demographic groups or stages of the disease. The strength of the correlations and the effect size will show the predictive outcomes of baseline assessment on the disease's progression, providing valuable insights into the early predictor of the Alzheimer's disease trajectory, which aid in the identification of high-risk individuals for early intervention.

We also include the analysis with MRI images to observe the brain volume changes, in areas like the hippocampus and cortex, which is important for memory and cognitive functions. This integration allows us to visualize the structural correlates to cognitive scores, which adds depth to our understanding of how Alzheimer's disease progresses. For example, a patent with high baseline MMSE score and minimal atrophy in the hippocampus on them initialize MRI scan show significant atrophy in follow-up scans, which correlates with a drop in MMSE scores. The analysis of the MRI images also allows us to perform subgroup analysis to explore how correlations between structural brain changes and cognitive decline vary across different demographic groups or disease stages.

Data collection and Preprocessing: Our dataset includes data from Alzheimer's patients. The preprocessing step was to ensure that the data is handled with missing entries and to ensure the standardized format across various entries. We are also involved in verifying that data handling is performed with participant consent. We also utilized advanced techniques such as machine learning algorithms to quantify changes in the bran structure and to measure the size of specific brain regions affected by Alzheimer's disease.

Variable Selection and Categorization: From the data, we selected variables that were crucial indicators to cognitive decline, demographic factors, diagnosis confidence, and functional abilities. Variables were chosen based on their significance to the progression of AD.

Analysis of demographic: We performed a demographic analysis to understand the age, gender distribution within the group. The impact of the demographic characteristics on the disease progression were analyzed to identify any significant patterns.

Diagnostic Confidence and Revisions: We explore and analyze the confidence levels with each diagnostic to identify and understand the validity of initial diagnoses and the factor that contributes to change over time. We also utilize MRI data to perform correlation analysis and regression models to handle high dimensional data and assess the relationship between brain structural changes and AD progression.

Finding:

We utilize Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) as part of the baseline evaluation, which services as primary indicators of cognitive functioning development.

1) MMSE and Disease Progression: Our analysis of the data shows that the MMSE scores were correlated inversely with the rate of cognitive decline ($r = -0.65$, $p < 0.001$). Those that have baseline MMSE scores in lower quartile have shown to experience a decline rate that were 1.5 times faster than those with upper quartile. To be more specific, for every point decrease in MMSE at baseline, there was an acceleration in the decline rate, as measured in MMSE over subsequent years. This pattern remains significant even when controlling for age, suggesting that the initial cognitive status, as captured by the MMSE, is an important predictor of future cognitive resilience or vulnerability. We also observed that patients with lower quartile MMSE scores not only experienced faster cognitive decline but also showed more pronounced brain atrophy over time. This correlation between lower MMSE scores and increased atrophy was evident in the hippocampus, which is important for memory, highlighting the MRI's role in anatomical underpinnings of cognitive deterioration.
2) ADAS-Cog as a Predictor: For ADAS scores, we found that the score correlates with higher proportion with increased risk of progressing from mild cognitive impairment to Alzheimer's disease with Hazard Ratio of 1.11 per point increase, 93% CI: 1.07 – 1.15, $p < 0.001$. Additionally, baseline ADAS-Cog scores predicts that the slope of cognitive decline of beta = 0.11, SE = 0.01, $p < 0.001$, with higher score associated with steeper decline trajectory over the follow-up period. From this data, the ADAS-Cog scores show

that with higher baseline indicating worse cognitive function, were associated with more rapid progression to advanced stages of Alzheimer's disease. The ADAS-Cog scores is sensitive to changes that are not captured by the MMSE. This is a significant predictive aspect for assessing disease trajectory.

3) Rate of progressions: The analysis shows that individuals on initial cognitive performance in the lower quartile experienced an increase in risk of progression to AD compared to the higher quartile. Individuals with steeper initial decline often experience a plateau, indicating a potential period where intervention might be more beneficials. The MRI data shows the patterns of disease progression. Those with lower quartile of initial cognitive performance faced an increased risk of AD progression but also shows significant rapid hippocampal atrophy within the first two years of follow up.
4) Cognitive and Functional Decline Correlation: The dataset variables related to cognitive and functional decline (DXCURREN, DXCONTYP) were cross analyzed with baseline measures, and the resulting correlation coefficient indicated a substantial predictive indicator for early cognitive score.
5) Demographic influences: Age appears as a string predictor when demographic variables were introduced into the analysis, with every six-year increase in age correlating with a 15% increase in the rate of cognitive decline. Gender also shows less predictive indicator for the diseases. Women, on average, shows a marginally slower progression to the severe stages of AD. Age indicates a string predictor of brain volume loss, aligning with the increased rate of cognitive decline. While gender had a less pronounced predictive value in cognitive assessment, MRI analysis revealed subtle differences in atrophy patterns between men and women, pointing to sex specific pathways in AD progression/

In our analysis of Alzheimer's disease progression using dataset, we analyze approximately 13525 entries to show patterns in cognitive and functional decline. The analysis is performed through dataset that focused on the baseline cognitive function that were measured by the Mini-Mental State Examination and functional abilities assessed through the Functional Activities Questionnaire. The finding shows that the average baseline MMSE score is 22, indicating mild cognitive impairment across the cohort. Patients with baseline MMSE scores of 20 or lower exhibited a 15% more rapid decline in their cognitive capabilities, in contrast with their counterparts with higher initial scores. An average baseline FAP score of 15, signaling some degree of functional impairments, was associated with a 35% acceleration in cognitive impairment tracked by both MMSE and Clinical Dementia rating (CDR) over the same period. The analysis also indicates that an increase in CDR from baseline correlated with a significant reduction in MMSE scores, averaging a two-point drop over the subsequent years, representing the progression in the severity of dementia. These result shows that there is a significant connection between initial cognitive and functional assessments and the predictor of Alzheimer's disease, showing the importance of early evaluation in informing treatment for these group of individuals with this condition to manage Alzheimer's disease effectively. The integration of MRI image analysis with cognitive and functional assessment offers compelling evidences of the structural brain changes with the AD progression. Thie comprehensive approach not only validates the predictive value of baseline cognitive scores but also shows the importance of early and accurate imaging diagnostics in intervention of Alzheimer's disease more effectively. The correlation between early MRI findings and subsequent cognitive decline highlights the importance of structural brain changes as

indicators of Alzheimer's disease, paving the way for intervention that could slow the progression of the disease.

Result:

The study analyzed data that focuses on the baseline cognitive/functional assessments and MRI-derived structural brain changes to understand the Alzheimer's disease progression. This highlights the relationship between the baseline cognitive and functional assessment scores and subsequent structural brain change as evidenced by MRI scans. This provides evidence for the relationship between clinical assessment scores and the underlying neuroanatomical alterations characteristics of Alzheimer's disease, offering a better view of the disease's trajectory. The inclusion of diverse participants, ranging from those at a preclinical stage of AD to those exhibiting advanced stages of cognitive decline, allowed for a robust examination of the disease across its spectrum. By using an approach to data preprocessing, ensuring the utmost data quality and integrity, we laid a solid foundation for our analysis. Utilizing sophisticated statistical methods, including correlation analysis and regression models, we discovered different relationships between various factors and the progression of AD disease. Our analysis not only highlights the predictive value of the baseline cognitive and functional scores but also highlights the significant role of MRI derived brain structural changes in understanding the AD progression. Through rigorous analytical process, we aimed to contribute valuable insights into the early predictor of AD disease trajectory, thereby improving the identification of high-risk individual for early intervention and informing more effective treatment strategies.

1. Cognitive Decline and MRI correlations:
    a. The correlation between cognitive decline and structural changes in the brain, as captured through MRI scans, shows a significant aspect of our analysis in understanding the AD progression. The data shows a striking association between baseline cognitive assessment scores.
    b. Hippocampal Atrophy and MMSE score: Our finding shows a pronounced hippocampal atrophy among participants whose baseline MMSE scores placed them in the lowest performance quartile. This group showed a significant 3% annual reduction in hippocampal volume, which is a key region implicated in memory formation and navigation. The rate of atrophy contrasts with the 1% decrease in participants with the highest MMSE scores, suggesting a correlation between cognitive performance and the rate of hippocampal degeneration. The accelerated cognitive decline observed in this group, with a 1.5-fold faster deterioration in MMSE scores compared to the highest quartile, underscore the hippocampus's vulnerability in Alzheimer's disease and its role in cognitive impairment.
    c. ADAS-Cog Scores and Cortical Thickness: Similarly, baseline ADAS-Cog scores provide insight into cortical changes associated with Alzheimer's disease. Participants with higher ADAS-Cog scores, indicating less cognitive function at the outset, exhibited reduced cortical thickness in the prefrontal and temporal loves. These regions are instrumental in executive functions and memory, highlighting the impact of AD pathology on brain areas critical for these cognitive domains. The inverse correlation between ADAS-Cog scores and cortical

thickness not only validates the ADS-Cog as a sensitive measure of cognitive impairment but also emphasizes the structural brain changes that accompany cognitive decline.

   d. Implication of MRI Correlations: Those correlations between baseline cognitive scores and MRI-derived measures of brain structure shows compelling evidence of biological understanding of cognitive decline in AD. The hippocampal atrophy correlates with lower MMSE scores, and the decreased cortical thickness correlated with higher ADAS-Cog score shows MRI scans can visualize the anatomical changes that reflect cognitive deterioration. This relationship highlights the potential of MRI as diagnostic tool, which is capable of identifying individuals at a higher risk of rapid progression, thereby facilitating early intervention strategies.

2. Impact of Demographic Variables: The impact of demographic variables, specifically age and gender, on AD progression offers valuable insights into how these factors influence that process. Our analysis highlights the important role of age as a determinant of structural brain changes, with a clear pattern of increased vulnerability to hippocampal atrophy and cortical thickness reduction as age advances.

   a. Age and its effects on brain structure: The finding that an increasing in age correlates with 1% increase in the rate of hippocampal volume loss and a decrease in cortical thickness. The reduction in cortical thickness, particularly in regions that is responsible for cognitive functions and memory, further exacerbates the cognitive decline experienced by patients. This age=related increase highlights the importance of early detection and intervention, especially as population ages.

b. Gender Differences in Alzheimer's Progression: The observation of gender differences in the pattern of brain atrophy adds another evidence of AD progression. While women showed a slower cognitive decline on average, the higher rate of hippocampal atrophy observed in female participants compared to the male counterparts is significant. This suggests that gender-specific biological that can influence the AD disease progression.

c. Broader Implications: the demographic impacts on AD progression, as revealed by the analysis, shows the need for an additional approach to AD research and treatment.

3. Functional Decline and MRI Fundings: The correlation between functional impairment, as measured by FAQ scores at baseline, and changes in brain volume presents evidence about the relationship between clinical assessments and neuroimaging findings in AD. Our analysis shows that participants with higher FAQ scores indicate higher functional impairment at the study outset, which experienced a greater reduction in the brain volume.

    a. Interpretation of Functional Decline and MRI Finding: The finding suggests that the degree of functional impairment provides a practical measure of how AD impacts everyday life. The strong correlations between higher FAP scores and the accelerated brain volume highlights the impact of functional decline on brain structures.

    b. Mechanism Underlying Functional Decline and Brain Atrophy: The mechanism behind this correlation may involve a cascade of neurobiological changes triggered by AD pathology, which contributes to ethe neuronal loss and brain

atrophy. As these features spread through the brain, they disrupt neural circuits that underline both cognitive functions and the ability to perform daily activities.

c. Clinical Implications: The predictive value of FQL scores regarding brain volume changes highlights the importance of incorporating functional assessment into the diagnostic and monitoring process for AD disease. By recognizing people with significant functional impairment as being at higher risk for rapid brain volume loss can inform treatment decisions, such as initiation of intervention aimed at slowing disease progression or addressing specific functional deficits. These relationship also highlights the need for holistic testing strategies that consider not only cognitive aspect but also functional abilities that is important for maintaining better life.