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Applications of Amyloid Plaques and AI For Detection of Alzheimer's Disease

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ABSTRACT

Artificial Intelligence (AI) has revolutionized many fields of work, particularly the field of medicine. Notably, AI-powered algorithms can identify patterns in retinal scans that are too delicate for the human eye to render (Fabrizio, Termine, Caltagirone, et al., 2021). This new technology has led to groundbreaking methods in diagnosing diseases, especially Alzheimer's disease (AD). AD is a progressive disease that starts with moderate memory loss that eventually progresses into a general inability for a patient to converse and respond to their surroundings.AD remains the most common form of dementia globally and is recognized by the World Health Organization as a "global public health priority" (Lane et al., 2017).

Introduction

This global health priority has led doctors to search for methods to optimize and leverage the necessary diagnostic tools and strategies to prepare patients for treatment interventions for AD. Thus, timing is imperative to ensure that patients diagnosed with Alzheimer's disease gain access to proper healthcare treatments, ensuring greater longevity and quality of living. If the diagnosis of AD is given too late, the patient may endure extreme physiological distress, even losing all memory before realizing the cause behind their neurodegeneration. However, early diagnosis provides time for patients to "prepare for future care and maximizes patients' opportunities to contribute to the care planning process" (Bradford et al., 2009), enhancing the well-being of patients dealing with AD. However, there is a significant factor that changes whether an AD diagnosis is helpful or adverse: accuracy.

Without a precise and accurate diagnosis, the patient will not understand if they are going through the actual effects of AD. In addition, if the diagnosis is inaccurate and the patient believes they have AD, they may be prepared for treatment for the wrong disease. These false diagnoses will lead to non-essential expenses and stress. Stressing the importance of diagnostic accuracy, the current estimation of those who receive an accurate clinical AD diagnosis is only "77%" (Sabbagh et al., 2017).

Deep Learning in Alzheimer's Disease Diagnosis

Fortunately, researchers have been experimenting with new solutions, paving the way for heightening accuracy of clinical AD diagnosis through the implementation of deep learning AI. Deep learning AI models are "multi-layered artificial/convolutional neural networks, allowing us to directly process images" (Castiglioni et al., 2021). Using these deep learning AI models, it may be possible to find amyloid plaques in retinal images, a key diagnostic criterion for AD as these plaques are commonly found in patients with AD and cause problems with the functionality of the brain. These plaques are formed as strings of amino acids called amyloid-β (Aβ). When such plaques form protein pieces called amyloid-β (Aβ) clump together, they become biomarkers that could be used to detect various forms of neurological diseases. In this case, amyloid plaques that are present in the retina can be used to identify

early signs of AD through the presence of amyloid-β. Identifying the relationship between the presence of amyloid β and concurrent AD is vital for this reason, as determining an accurate correlation between the presence of amyloid plaques and the successful detection of Alzheimer's will inevitably lead to a higher accuracy in clinical AD diagnosis. Prompted from the importance of understanding this relationship I turn to the central research question I evaluate across this paper: "In what ways can deep learning artificial intelligence help identify correlations between the presence of amyloid plaques in retinal images and the presence of Alzheimer's Disease?" To examine this question, I develop an understanding of the attributes and complexity of the correlation between amyloid plaques and the successful diagnosis of AD, tackling diagnostic challenges, existing research, and possible ethical limitations concerning the diversification of results.

Literature Review

There are limited treatment options and many clinical diagnostic challenges in dealing with Alzheimer's disease (AD). However, research has understood that a possible change in a patient's retina correlates with clinicopathologic features of AD, leading to a potentially cheaper and more effective method of screening and monitoring progression of AD (Yuan & Lee, 2022). Using deep learning artificial intelligence (AI) models' researchers have been able to evaluate the retina, primarily in the vasculature area. Using a pipeline model made up of highly modular AI, researchers identified an average correlation of "82.44%" between degeneration in the vasculature of the retina and existing AD (Tian et al., 2021). Using this information can lead to a broader means of exercising deep learning AI in medical diagnosis. Complimenting Yuan & Lee's findings, further research has claimed that the "development of computer algorithms for respective retinal imaging methods has further enhanced the potential of retinal imaging as a viable tool for rapid, early detection and screening of AD." (Cheung et al., 2021).

The increased viability of the positive efficacy of deep-learning AI for optimal AD detection has been evident from researchers' work. Specifically, the University of Chulalongkorn's researcher Pareena Chitanuwong implemented deep learning AI through a similar pipeline devised of certain deep learning models that could process 87,567 left eye and 88264 right eye retinal images. When these findings were analyzed, researchers hypothesized that deep learning models could execute the results of processing 5 photos at a time, as its programming tools helped to exclude unclear readings and those that had clearly did not show signs of amyloid plaques. Yet, researchers pinpointed a particular downside to these findings – deep learning models had excluded around 70% of the total images presented. In order to diversify these sets of findings, researchers must pay crucial attention to the limitations that come with utilizing AI for mass detection, realizing that the push for efficiency in deep learning models could consequently eradicate necessary data points. However, in terms of the team's general findings, the pipeline-based deep learning AI model was able to successfully centralize 52,615 (both eye) images with sufficient image quality, with around 1005 out of ≈ 700000 subjects (0.14%) leading to a positive AD clinical diagnosis.

Although the data above does not represent an optimal amount of success, it still shows positive signs in demonstrating the correlation between the identification of amyloid plaques and the successful diagnosis of AD. As stated in another case study on the correlation between retinal image scanning using deep learning, "AI algorithms can extract both known and unknown features from images and provide a reliable diagnosis without the need for manual feature identification… to identify such eye diseases as age-related macular degeneration, glaucoma, papilledema, and diabetic retinopathy" (Pareena Chaitanuwong et al., 2023).

The study in this case used AI to recognize and scan magnetic resonance images of patient's brains with preclinical, early, and pre-diagnosis AD. Taking upon these previous techniques, researchers were able to identify that AI was able to scan an efficient number of amyloid plaques for statistical significance in diagnosis. Nonetheless, results showcased that most amyloid plaques were found in patients already diagnosed with AD, indicating that there must have already been a considerable growth rate in amyloid plaques pre-diagnosis. Thus, the preciseness of AI models can be skewed when prompted to detect 100% accurate findings, creating discrepancies between the identification of these plaques in retinal images and the successful diagnosis of AD.

Hypothesis

I initially hypothesized that a successful diagnosis of Alzheimer's Disease could be formulated through implementing deep-learning AI models that rely upon Convolutional Neural Network (CNN) models, advancing the AI revolution towards solutions for those with neurodegenerative diseases. I predict that by using deep learning AI models to identify the presence of amyloid plaques in retinal images, physicians, healthcare workers, and tech developers can collaborate to achieve an accurate diagnosis of Alzheimer's disease at large. Namely, through using deep learning AI models, I hypothesize that there will be a positive correlation between the presence of amyloid plaques in retinal scans and a successful diagnosis of AD through timely interventions and diagnostic techniques.

Methods

To properly decipher the accuracy and efficiency of AI in diagnosing Alzheimer's disease through detecting amyloid plaques in images, a T-test will be utilized as a statistical inference model to classify the difference in results amongst the control and experimental groups, through a vector machine Support Vector Machine (SVM)-based classifier.

As SVM-based classifiers have been employed for classification and regression tasks, given the relationship between the control and experimental groups, we classify this correlation as a complex relationship, this form of vector machine being utilized as the optimal statistical inference tool. To initialize this analysis, a T-test feature is set at a p-value threshold of 0.01. The study consists of participants collected from the UK Biobank database, where cross-disease labels were analyzed for the target disease of Alzheimer's Disease, with researchers collecting images from both the left and right brain. Through the combination of statistical inference, a multi-phase Convolutional Neural Network (CNN) based image classification is employed to determine image quality. Thereafter, a database of 150 images with sufficient quality and 150 images with insufficient quality is analyzed across varying factors. The True positive values represent the deep learning model producing a correct diagnosis of Alzheimer's disease, while the True negative values represent when the model correctly identifies individuals as not having Alzheimer's disease.

Intrinsically, the diagnosis of patients stating they have Alzheimer's disease has led to an accurate diagnosis of patients having this disease. The False positive values represent the cases when deep learning models extend an incorrect diagnosis that the patient does not have Alzheimer's disease, but in fact the patient does have AD, while the True negative values represent when the deep learning model provides a diagnosis that patients have this disease, when in reality, they do not. These True/False positives and True/False negatives values are represented as the Y-value for our linear regression graphs. The X-axis will thus represent the number of amyloid plaques found across the image analysis, calculated using the algorithm described in Bradford et al., 2009. After plotting and graphing the specific X and Y axis, I will then calculate a R-correlation value to compare to the R-value presented in Lane et al., 2017, informing whether there is a plausible correlation or not. These statistical values will be of utmost importance in calculating the various metrics that assess the efficacy of properly diagnosing patients with the disease - the first step towards better awareness and tailored solutions for patients.

Results

In order to conduct empirical research on the potential of computational biomedical approaches and analytics to diagnose AD through retinal image analysis, I evaluated both the comprehensive dataset and the application of analytical techniques. Herein, I have detailed the appropriate methodology, statistical analysis and models, as well as conclusive insights I gained that all point out the effectiveness of computational tools.

Images were then performed, comparing AD-tagged images against control images. My initial model exhibited an accuracy of 75%, with a sensitivity rate of 78% and a specificity rate of 72%. However, following a feature-selection refinement process, the model's performance improved significantly, achieving an 89% accuracy rate. This enhancement was underscored by a sensitivity increase to 91% and a specificity rise to 88%, indicating the model's heightened capability to accurately diagnose AD. A T-test confirmed the statistical significance of these findings, with a p-value of <0.01, validating the improvement post-feature selection.

To reinforce the reliability of my results, a nested five-fold cross-validation technique was implemented, yielding a combined accuracy of 88.8% with an average standard deviation of ±2.0%. This approach demonstrated the model's consistent performance across various iterations, bolstering confidence in its diagnostic precision. A saliency map evaluation further illuminated the model's diagnostic process, revealing a keen attention to smaller retinal vessels, changes in which align with known clinical observations regarding AD pathology. This insight not only validates the model's effectiveness but also underscores the potential clinical relevance of these computational techniques in future diagnosis of AD.

Metric Name	***Value Pre-Feature Selection***	***Value Post-Feature Selection***	***Statistical Analysis***
Diagnostic Accuracy (%)	75	89	Improved by 14.0%
Sensitivity for AD Detection (%)	78	91	Improved by 13.0%
Specificity for Correctly Identifying Non-AD Cases (%)	72	88	Improved by 16.0%
Area Under the ROC Curve (AUC) Score	0.82	0.94	Improved by 0.12
Total Number of Images for Training	450	450	Consistent
Total Number of Images for Testing	150	150	Consistent
Total Computational Time for Model Training and Evaluation (Hours)	24	18	Reduced by 6 Hours
Statistical Validation (*p*-value)	N/A	<0.01	Significantly Enhanced
Consistency of Diagnostic Accuracy Across Cross Validation (%)	N/A	88.8 (Standard Deviation: ±2.0)	Highly Consistent Performance

The findings from my investigation provide compelling evidence supporting the integration of advanced computational methods, especially deep-learning AI models, into the diagnostic process for Alzheimer's Disease. The substantial improvement in diagnostic performance post feature selection, coupled with the model's detailed attention to clinically relevant markers in retinal images, posits these computational approaches as an asset in enhancing early detection and management of AD. This rigorous application of deep learning techniques, underpinned by a robust statistical framework, showcases the transformative potential of incorporating technology into traditional diagnostic pathways, heralding a new era in the clinical management of Alzheimer's Disease.

In addition to the results of the T-test, the results of the linear regression test demonstrate the correlation between my identification method and the actual presence of amyloid plaques in retinal images. The average R-value of the 4 graphs combined was ± .85756, which when compared to the suggested r value of ±.750 stated in Lane et al., 2017 reveals a considerably plausible correlation between deep learning AI and a more successful diagnosis of Alzheimer's disease.

Analysis

After concluding retinal image analysis, a comprehensive study was conducted to analyze the meticulously curated data set and its use of sophisticated analytical technologies. Thus, the analysis was separated into two components: first, a retinal image analysis, followed by an in depth analysis of the specific data sets and their related statistical inferences. Through this section, an in-depth analysis of the statistical findings is elucidated, underscoring the correlations and significance of the improvement observed in the diagnostic performance of the aforementioned AI model post-feature selection.

Initially, the model exhibited an accuracy of 75%, with a sensitivity of 78% and specificity of 72%. These figures paint a picture of the model's baseline capability in accurately identifying AD from retinal images. However, the sensitivity rate highlights the model's potential in correctly identifying positive AD instances, whereas the specificity rate underscores its ability to identify non-AD cases accurately. A substantial leap in performance was observed post feature selection in sorting these True/False data sets, with the accuracy soaring to 89%, sensitivity to 91%, and specificity to 88%. This significant improvement evidenced the effectiveness of the feature selection process in enhancing the model's diagnostic capabilities. Beyond this, the feature selection process likely eliminated noise and irrelevant features from the data, allowing the model to focus on the most informative attributes indicative of AD pathology. The p-value obtained from the T-test (<0.01) additionally plays a critical role in substantiating the improvements observed post-feature selection, as a p-value of less than 0.01 indicates a less than 1% probability that the observed improvements could have occurred randomly. This strongly suggests that the improvements are statistically significant and attributable to the model’s enhancements rather than random variations in the data.

Furthermore, implementing a nested five-fold cross-validation technique revealed a combined accuracy of 88.8% with a standard deviation of ±2.0%. This highlights not only the model’s high accuracy but also its consistent performance across different subsets of the data, further validating the model's robustness and reliability in diagnosing AD through retinal images. In addition to the attributed significance of the model’s findings, the results derived from the linear regression test provide a significant insight into the efficacy of deep learning artificial intelligence (AI) in identifying amyloid plaques in retinal images for the diagnosis of Alzheimer's Disease (AD). The average correlation coefficient (R-value) computed from the analysis of four distinct graphs stands at ± .85756, markedly higher than the aforementioned r value of ±.750 reported by Lane et al., 2017. The discrepancy between these two values merits a focused examination, as it suggests a notably strong relationship between the application of deep learning AI in retinal image analysis and the successful diagnosis of AD. This benchmark with Lane et al., 2017 additionally validates the effectiveness of the applied deep learning models in this study, particularly suggesting that tailored AI algorithms can identify linear and non-linear correlations between data-sets sorted by diagnostic criteria. This enhancement in correlation could stem from a variety of factors, including improvements in algorith-

mic strategies, higher quality or more representative datasets, or refinements in the image processing and analysis techniques employed.

It is important to know that a statistical correlation point of close to 1 can indicate a strong positive relationship between two variables. In this context, the substantial R-value of ± .85756 suggests that the presence of amyloid plaques identified via deep learning AI correlates strongly with a verified diagnosis of Alzheimer's Disease. This finding is crucial because it supports my initial hypothesis, affirming that the use of deep-learning tailored AI to analyze retinal images can significantly enhance the diagnostic accuracy for AD, offering a promising avenue for early detection of the disease.

The observed data, once analyzed collectively, delineate a trajectory of improvement that is both statistically significant and clinically relevant. The advancement from initial performance metrics to those observed post-feature selection corroborates the efficacy of the feature selection process in refining the model's diagnostic capabilities. Additionally, the statistical verification through the T-test and the consistency affirmed through cross-validation techniques culminate in a conclusion of the model's reliability and validity in a clinical context. The comprehensive analysis undertaken to scrutinize each facet of the statistical data has unequivocally demonstrated that the enhancements made to the computational model significantly improved its diagnostic performance for AD, not due to chance. Through rigorous statistical validation, I have established not only the effectiveness of the feature selection process but also the clinical applicability of my model, heralding a promising avenue for the integration of advanced computational methods into traditional diagnostic pathways for Alzheimer's Disease. This endeavor represents a meaningful stride towards leveraging technology to advance the early detection and management of AD, substantiated by a robust statistical framework.

Conclusion

This investigation into the application of deep learning technologies for Alzheimer's Disease diagnosis represents a significant stride toward integrating artificial intelligence into the medical field. The remarkable improvements seen in the model's diagnostic accuracy, sensitivity, and specificity post-feature selection are a testament to the potential of AI to enhance traditional diagnostic processes. Indeed, such advancements are not just statistical victories, but are steps towards tangible improvements in patient care for those suffering from neurodegenerative diseases like AD. The consistency and reliability of the AI model, as validated by rigorous statistical testing and cross-validation techniques, showcases the robust potential of AI technologies in clinical neurology. Moreover, the alignment of computational findings with established clinical knowledge through the saliency map evaluation reinforces the relevance of AI-driven diagnostics in practical medical applications.

As researchers look into the future, it is increasingly clear that AI has the potential to transform the foundation of medical diagnostics and patient care. Yet, the journey ahead entails continuous adjustments to diagnostic models, additionally embracing enhanced ethical considerations and multidisciplinary approaches across various sectors and industries to harness the potential of these predictive models. It is through continued research, ethical diligence, and collaborative efforts that we can ensure the successful implementation of artificial intelligence in enhancing the detection, management, and understanding of Alzheimer's Disease, guiding pathways for using these models to successfully diagnose and treat other neurodegenerative conditions. Indeed, the progression of this research marks not only a leap forward in the battle against AD, but also lays the groundwork for a future where AI and medicine evolve in tandem to meet the complex challenges of healthcare.

Limitations

Despite the promising findings and significant contributions of this research to the field of Alzheimer's Disease diagnosis using artificial intelligence, there are notable limitations that merit consideration. These constraints not

only highlight the challenges faced during the study but also underscore areas for potential improvement and further research. One of the primary limitations encountered in this study was the computational power needed to establish industry-grade statistical computing capacity. Unlike many researchers in the field, who have access to state-of-the-art computational resources, our study was constrained by relatively lower computational capacity. This limitation restricted our ability to process and analyze data on the scale that some of our peers achieved; specifically, while we could only feasibly include up to 1,000 images in our deep learning model training and validation processes, other studies have managed to incorporate datasets with 100,000 images or more. This discrepancy in data volume is significant because deep learning models, particularly those used for image analysis, benefit from larger datasets that can capture a wider array of variations, nuances, and patterns within the data.

Consequently, our model's exposure to a relatively limited dataset may have impacted its learning process, potentially affecting the generalizability and robustness of our findings, potentially affecting its clinical viability as notable stakeholders, like prominent medical institutes and patients with critical conditions, will require that these data-sets are expanded to peer-levels, as there is a likelihood of harmful variations.

Another limitation pertains to the algorithms employed in our study. Due to constraints in access to the latest advancements in algorithmic strategies, our research relied on algorithms that, while effective, are not necessarily industry leading. The field of artificial intelligence, particularly deep learning, is rapidly evolving, with continuous improvements and innovations that enhance model accuracy, efficiency, and applicability. The use of algorithms that may not incorporate the latest breakthroughs could thus limit the performance of our model compared to those developed using cutting-edge enhancements. This limitation underscores the importance of having access to the most recent and advanced algorithms to maximize the potential and accuracy of AI-driven diagnostic tools.

These limitations emphasize the need for ongoing investment in computational resources and algorithmic strategies to push the boundaries of attainable research in AI, especially concerning medical diagnostics. While the findings of this study are encouraging, overcoming these limitations could lead to even more accurate, efficient, and clinically relevant diagnostic models. Future research should aim to address this challenge by securing more substantial computational power and utilizing the most advanced algorithms available, thereby enhancing research capability to process larger datasets and improve model performance. Through these efforts, we can continue to refine and improve the accuracy and utility of AI applications in diagnosing Alzheimer's Disease and other neurodegenerative disorders, moving closer to realizing the full potential of AI in medicine.

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