HIGH SCHOOL EDITION
Journal of Student Research
Volume 13 Issue 4 (2024)

Identifying Progression Pattern of Alzheimer's Disease Using Longitudinal Clinical and Neuroimaging Biomarkers

Ann Song

Choate Rosemary Hall, USA

ABSTRACT

Alzheimer's disease is one of the most common neurodegenerative disorders worldwide. Therapeutics to treat or prevent Alzheimer's disease progression has not been successful due to the possible heterogeneity of progression and response to treatment. The goal of this study was to determine whether there is a common pattern in Alzheimer's Disease progression that can be used to guide the clinical trials and treatment. Longitudinal clinical and neuroimaging biomarkers data from Open Access Series of Imaging Studies were analyzed using an approach based on Mixture of Gaussian Processes Model to identify clusters that has similar pattern in progression. The approach enables non-parametric analyses with no assumptions on linearity and number of clusters. It was demonstrated that normalizing the patient's own onset value yields better accuracy in stratifying patients by progression rate because it removes the systematic variations and imbalance induced by environmental and genetic differences among the patients. The clustering result showed that the Alzheimer's Disease progression is nonlinear, suggesting that the initial progression rate should not be used to evaluate the future progression trajectory. It was demonstrated that the progression is heterogeneous among the patients within each biomarker and among biomarkers of each patient, indicating the importance of personalized treatment for individual patient. Additional analyses with more data to ensure the robustness of the clustering will provide neurologists a powerful tool to estimate the progression trajectory of each patient, with which a personalized treatment becomes possible.

Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders worldwide, with a prevalence of 3.9% for individuals over the age of 60 (Prince et al., 2013). Despite the availability of several drug therapeutics to treat AD or delay its progression from Mild Cognitive Impairment (MCI), around 12–15% of individuals with MCI progress to AD annually(Petersen, 2004). Failure of drug therapeutic attempts is partially attributed to the heterogeneity of progression and response to treatment (Goyal et al., 2018; Mehta et al., 2017).

Researchers commonly use longitudinal functional clinical biomarkers to assess the AD progression. The neuropathological hallmarks of AD mainly include amyloid-beta (Aβ) plaques and neurofibrillary tangles of hyperphosphorylated tau, which are believed to result in structural neurodegenerative changes in the brain (Deture et al., 2019; Meyer et al., 2020). Both linear and non-linear progression of cognitive decline in AD patients has been reported with different progression profiles among individuals (Doody et al., 2010; Stern et al., 1996). Measurement and modeling of these biomarkers have significantly helped diagnoses and treatment strategies. However, the heterogeneity of progression is still not understood as individuals are often evaluated at different stages of the disease, and there are systematic variations due to environmental and genetic differences, making the comparisons among all the patients challenging.

It is critically important to identify progression patterns of AD because it would be the first step to personalized treatment for patients based on their pattern. The application of precision medicine with AI techniques is emerging

as a promising approach for preventing disease progression and improving treatment outcomes (Silva-Spínola et al., 2022). The implementation of machine learning techniques to analyze large-scale multi-modal data within the framework of precision medicine would improve the ability to design research that aims to determine disease progression mechanisms. Furthermore, it would aid in guiding clinical trials with variations of environmental, genetic, and other factors in mind.

Several models have been developed to understand AD progression. However, most models only use a small subset of available biomarkers (Jack, Knopman, et al., 2013; Jack & Holtzman, 2013). My previous research identified several significant clinical and neuroimaging biomarkers that correlate with the patients' cognitive status. These biomarkers include the deposition of amyloid-beta (Aβ) plaque and the volume or thickness of certain brain regions. A model that incorporates all these multimodal variables would provide a more comprehensive insight into AD progression.

In addition, previous studies that model AD progression were limited by parametric assumptions on abnormalities or outcome measures (Doody et al., 2010; Fisher et al., 2019; Goyal et al., 2018; Peterson et al., 2018). For example, Peterson et. al. used a Gaussian Process model (pGP) to predict key metrics of AD progression (Peterson et al., 2018). However, it was assumed that each patient followed a single progression path with noise, which artificially removes the heterogeneity of the progression. With the complexity of AD progression, it is critical to develop computational methods that can flexibly identify patient clusters with minimal assumptions.

The goal of this study was to determine whether there is a common AD progression pattern that can aid in guiding clinical trials and treatment. An approach based on the Mixture of Gaussian Processes Model (MoGP) was used to identify clusters that show similar progression patterns (D Ramamoorthy et al., 2022; Divya Ramamoorthy et al., 2022). The MoGP model involves two Bayesian non-parametric methods: Gaussian process regression (C. E. Rasmussen et al., 2005; C. Rasmussen et al., 2001) and Dirichlet process clustering (Albert, 1984; Escobar et al., 1995). Gaussian process regression allows for the learning of progression patterns from data without a predefined function form; therefore, it can capture all possible progression patterns (D Ramamoorthy et al., 2022; Divya Ramamoorthy et al., 2022). The Dirichlet process clustering method has the advantage of identifying clusters with no assumptions on the number of clusters needed.

Methods

Study Design

Data used in this study were obtained from the Open Access Series of Imaging Studies (OASIS-3) (LaMontagne et al., 2019). Data of patients that show progression from CN or MCI to AD were used for the analyses, including Amyloid Centiloid PET imaging data and brain volume characterized by Brain MRI imaging. The biomarkers identified to be the greatest impact on AD progression from previous studies were analyzed to determine the progression pattern (Song, 2022). MoGP for sparse longitudinal data was used to process the progression (Fraenkel, 2022).

Data

OASIS-3 is longitudinal data including 2842 MR Sessions, 2157 PET Sessions, and 1472 CT Sessions from 1379 participants, which include 755 cognitively normal adults and 622 individuals at various stages of cognitive decline ranging from 42 - 95 years old. For more detailed statistics of OASIS-3, please refer to the literature (LaMontagne et al., 2019). The OASIS-3 data are hosted on XNAT Central (https://central.xnat.org), a publicly accessible data repository.

The data reported in OASIS-3 include patient demographics, family history, patient physical and medical history, Clinical Demential Rating (CDR), dementia staging, Mini-Mental State Examination (MMSE), clinical diagnosis, Amyloid Centiloid values by PET imaging and Brain volume by MRI imaging.

Data Preparation

To apply the MoGP model, the relevant biomarker data from OASIS-3 needs to be processed into two 2D arrays:

- The first is a time array. Each patient is represented by a row, with columns indicating time since symptom onset $t = 0$). All times are in years since the first visit.
- The second is an array for the value of each biomarker used in the study. Like the time array, each patient is represented by a row. Columns include the values of MMSE and cortical volumes and thicknesses that were identified to be the most important biomarkers from the previous study (Song, 2022), including Left Nucleus Accumbens Volume, Left Amygdala Volume, Left Hemisphere Middle Temporal Thickness, Left Hemisphere Superior Temporal Thickness, Right Amygdala Volume, Right Inferior Lateral Ventricles Volume, Total Hippocampal Volume. The Mean Cortical Amyloid Centiloid was not used in this study because most of the patients only have 1-2 data points reported by OASIS-3 database. CDR is not analyzed either because the values are not continuous, which is not suitable for a MoGP model application.

Only patients who showed progression were chosen from the data to be used in this study. The onset value of a symptom is determined by the biomarker value that corresponds to the last year when a patient was diagnosed with CN before being diagnosed with MCI or AD. If a patient is diagnosed with MCI or AD on their first visit, then the data from their first visit will be considered their onset value. In a study on amyotrophic lateral sclerosis (ALS) progression analyzed by previous studies using the MoGP model (D Ramamoorthy et al., 2022; Divya Ramamoorthy et al., 2022), the onset of the ALS system has a fixed value. In this study, however, the onset value of each biomarker has a great variation among patients (Figure 1 and Figure 2). To remove the effects of the variations of the onset value on clustering, the values of each patient at different visit times were normalized by the onset value, which resulted in the onset value for each patient being 1 for all the biomarkers (Figure 3).

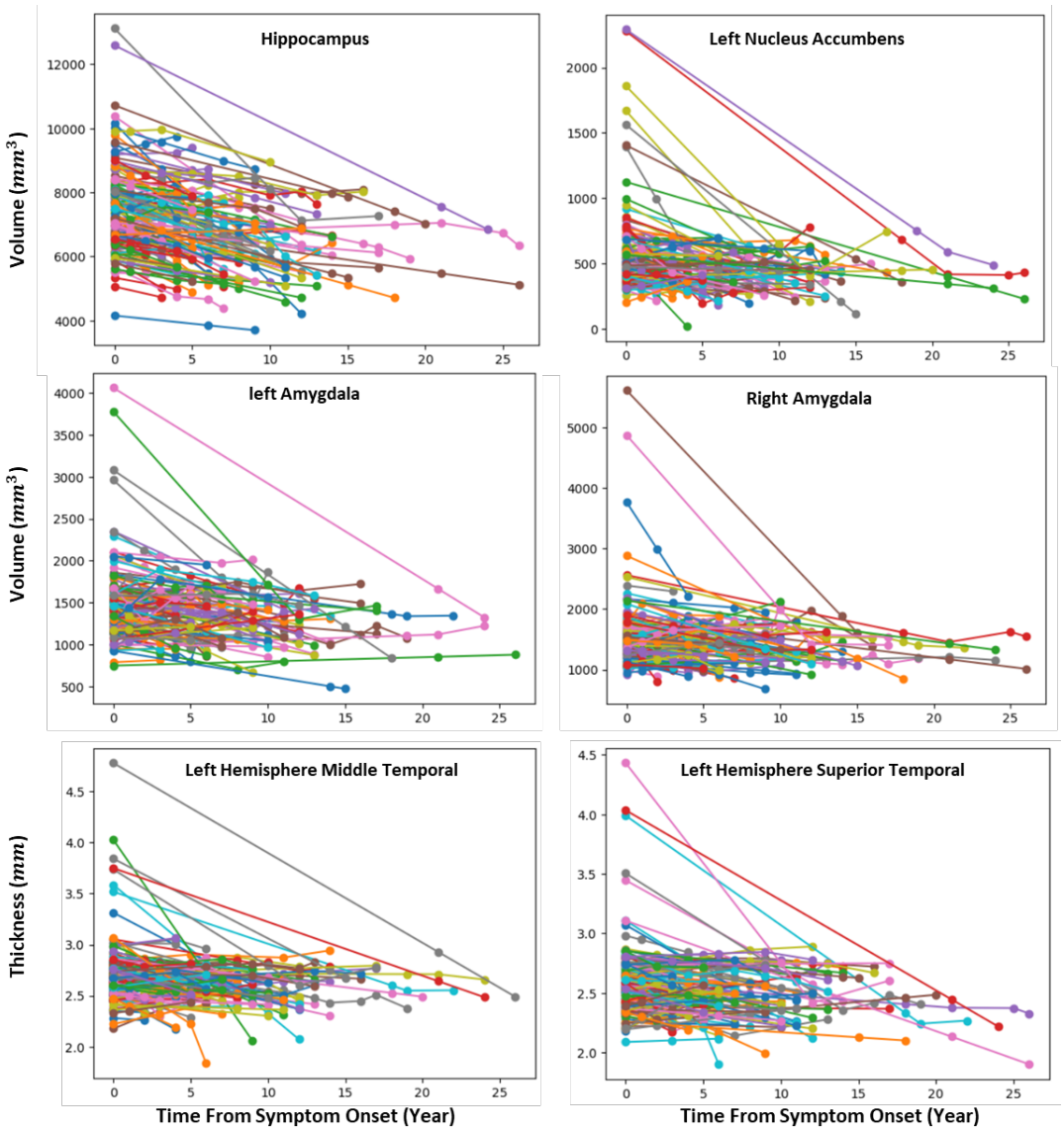

Figure 1. Absolute values of biomarkers VS. time. Each line represents each patient in the plots.

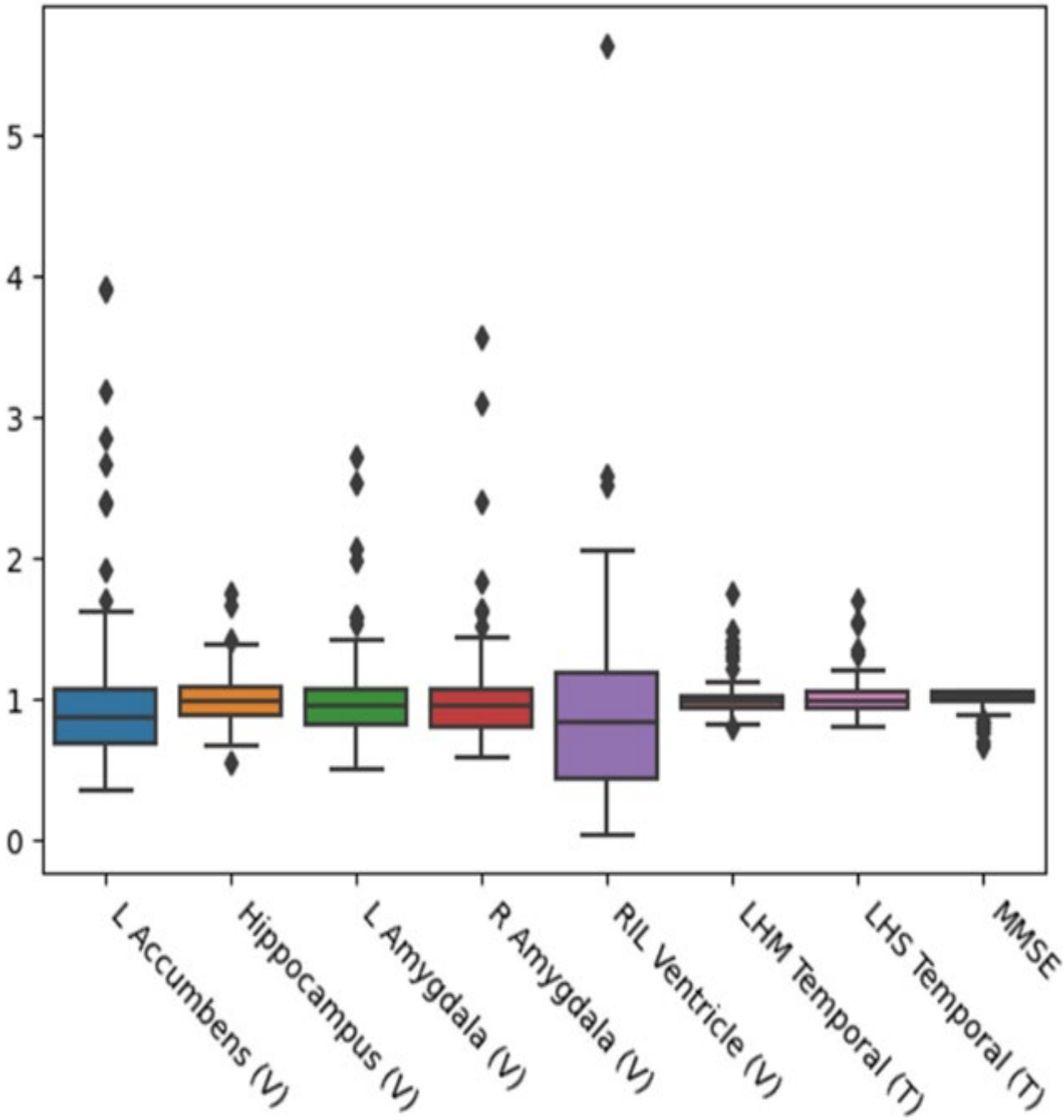

Figure 2. Boxplot of the onset values of each biomarker. The values are all normalized by the mean value of each biomarker to fit all the biomarkers in one plot. L: Left; R: Right; I: inferior; M: middle; S: superior; V: volume, T: thickness.

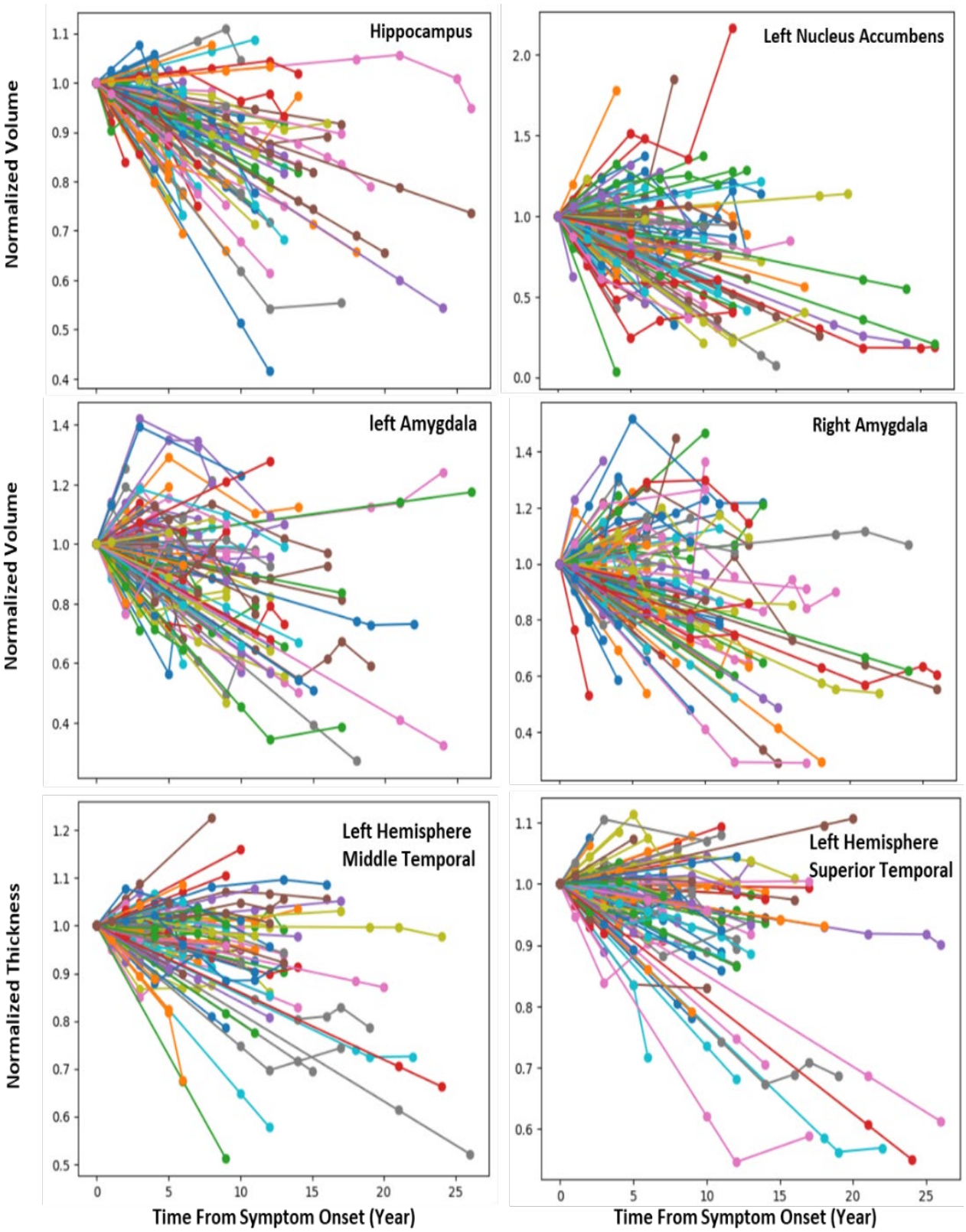

Figure 3. Biomarker values normalized by the onset value of each individual patient.

Modeling

The MoGP model uses Gaussian process (GP) regression and Dirichlet process (DP) clustering. The Gaussian process is a nonparametric supervised learning method used to solve regression and probabilistic classification problems regression (C. E. Rasmussen et al., 2005; C. Rasmussen et al., 2001). Gaussian processes have priors that define the user's expectation specified by a mean function and covariance kernel (Hackeling, 2017): $f(x) \propto GP(m(x), k(x, x'))$, where $m(x)$ is the model's mean function and $k(x, x')$ is the model's covariance function. With the expectation of continuous trajectory, a squared exponential (SE) kernel was used, as explained in literature (Fisher et al., 2019; Goyal et al., 2018), $(x, x') = \sigma^2 exp \frac{-(x-x\prime)^2}{2l^2}$, where σ^2 is the model's covariance that determines the average distance of the function from the mean and l is the characteristic length-scale of the process. The length scale defines how close two points must be to influence each other significantly. Therefore, it specifies the smoothness of the function, i.e., the larger the length scale is, the smoother the function is. In this study, a gamma prior with a mean of 8 and variance of 5 was used for the length scale based on the data.

Dirichlet process mixtures is an unsupervised learning model that can be used to identify a cluster without making any assumptions on the number of clusters in advance. The process begins with assuming that there could be an infinite number of clusters. It then narrows down the prediction by considering several mixture components provided by the Gaussian Process. The patients' trajectories are then grouped into different clusters based on the probability of explaining the progression best (D Ramamoorthy et al., 2022).

Model Evaluation

The average first year slope of each cluster was calculated and plotted to evaluate the trajectory nonlinearity. The slope was calculated as the slope of the line between the onset value at $(t = 0)$ and at $(t = 1)$. The average Root Mean Square Error ($RMSE = \sqrt{\frac{\sum_{i=1}^{N}(y(i)-\hat{y}(i))^2}{N}}$) of all the test data was used to evaluate the accuracy of the model. The lower the RMSE is, the higher the prediction accuracy is.

Results

Variations on the onset value (Figure 1) and the progression speed (Figure 3) are shown among all patients. For instance, while certain patients exhibited rapid progression, they had high initial biomarker values. As a result, even after some progression, their biomarker values were still greater than the onset value of other patients, influencing the clustering outcomes and the size of each cluster. Normalizing the data by the onset value of each patient removes the onset variations among patients. Therefore, clustering can focus on progression speed instead of absolute values of each biomarker.

Clustering based on both normalized and non-normalized data resulted in multiple clusters. The top 3 clusters from both methods from the example biomarkers are shown in Figure 4. It shows that modeling with normalized values yields more distinct clusters with fewer overlaps among them. As expected, clustering with normalized data results in a decrease in RMSE error while predicting progression values (Figure 5). This was the result of variations of onset values being removed. The results presented in Table 1 demonstrated that clustering with normalized data significantly reduces the error in predicting progression values.

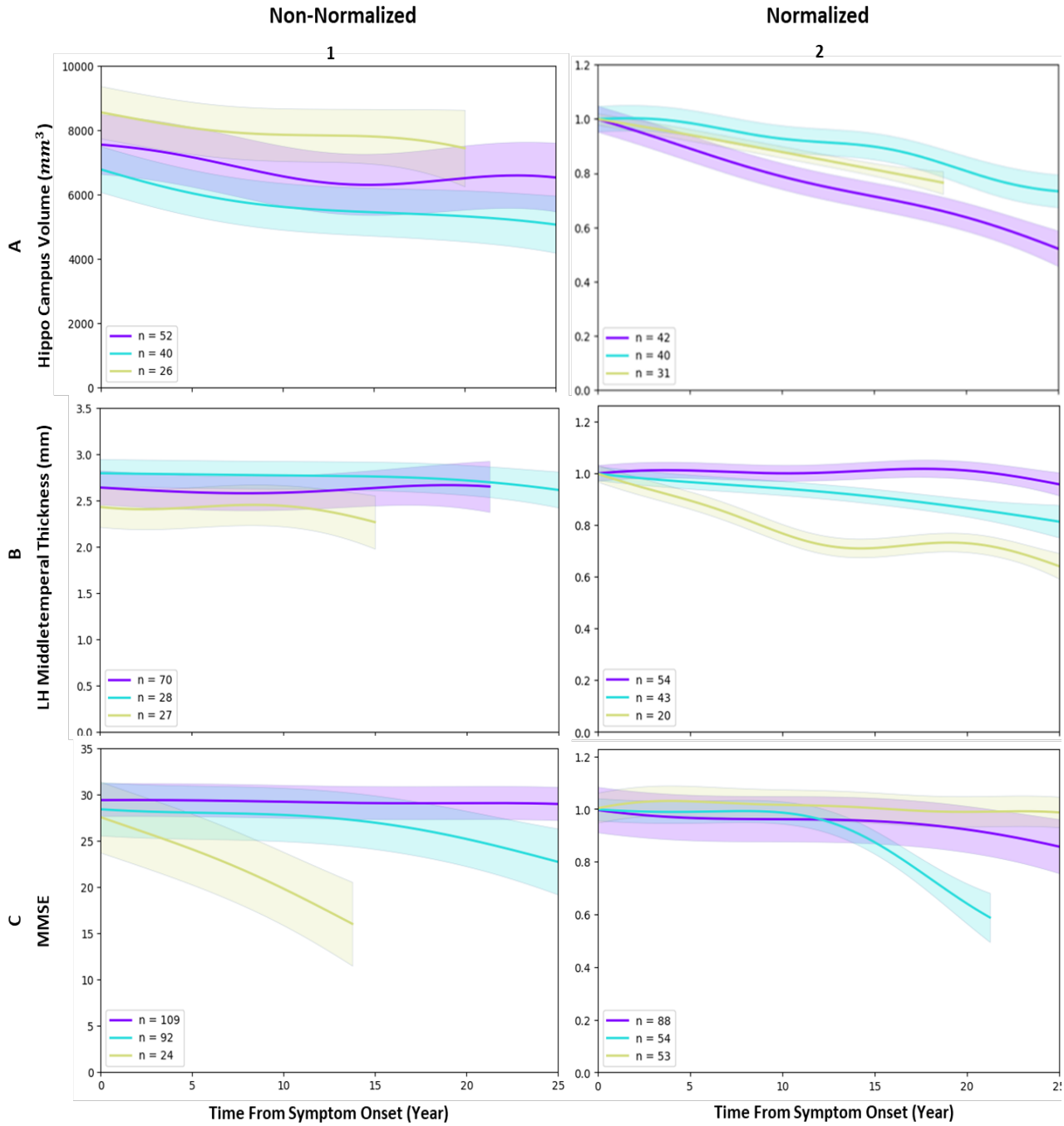

Figure 4. Example Top 3 clusters from non-normalized vs normalized data. The number of n indicates the number of patients in the corresponding cluster. LH: Left Hemisphere.

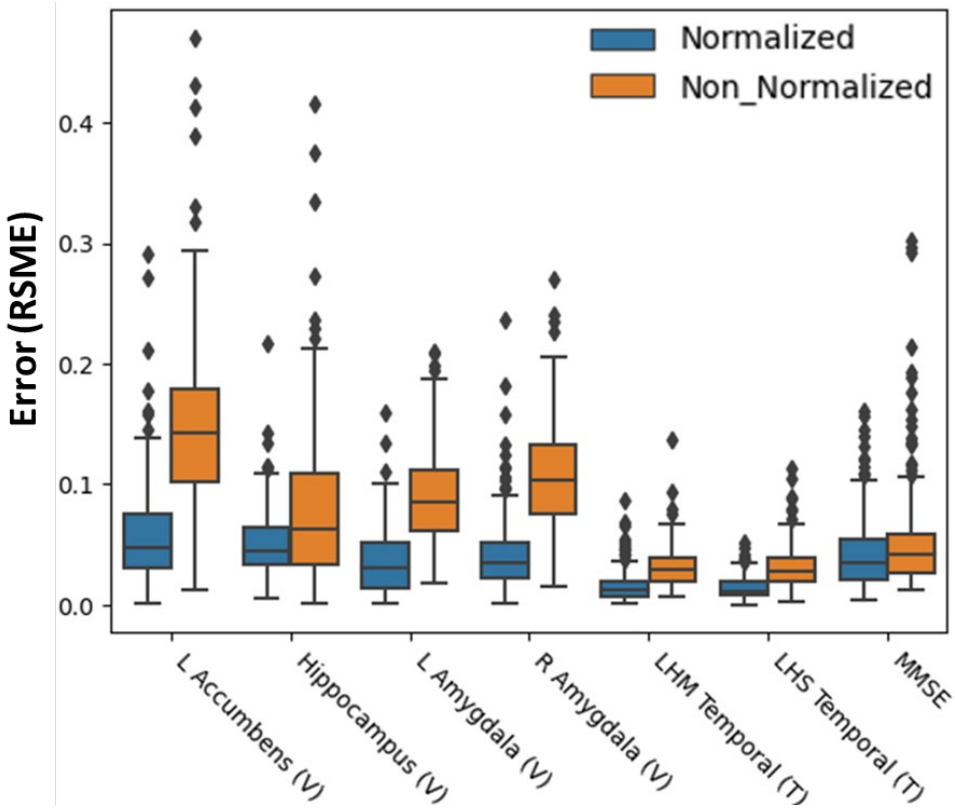

Figure 5. RMSE Error for non-normalized vs normalized data. For the error of the non-normalized data, the RMSE error was normalized by each patient's onset value for a fair comparison between the methods. L: Left; R: Right; H: Hemisphere; I: Inferior; M: Middle; S: Superior; V: Volume; T: Thickness.

Table 1. Prediction RMSE Error of clustering using normalized data vs. non-normalized data. L: Left; R: Right; H: Hemisphere; I: Inferior; M: Middle; S: Superior; V: Volume; T: Thickness

Biomarkers	RMSE (Data Normalized)	RMSE (Data Not Normalized)	p-value
LN Accumbens (V)	0.059 +/- 0.048	0.150 +/- 0.076	1.62E-24
Hippocampus (V)	0.051 +/- 0.028	0.083 +/- 0.072	8.48E-07
L Amygdala (V)	0.038 +/- 0.029	0.090 +/- 0.041	1.29E-27
R Amygdala (V)	0.043 +/- 0.035	0.106 +/- 0.048	2.08E-30
LHM Temporal (T)	0.015 +/- 0.014	0.032 +/- 0.018	3.67E-16
LHS Temporal (T)	0.015 +/- 0.010	0.032 +/- 0.019	2.60E-19
MMSE	0.041 +/- 0.028	0.051 +/- 0.041	8.12E-04

Nonlinearity in the progression of all the biomarkers was observed. As shown in Figure 6 and Figure 7, none of any clusters of any biomarkers show a linear progression that aligns with the initial progression slope. For example, the initial progression of some clusters showed an increasing trend, while the corresponding clusters showed a decreasing trend. This suggests that the initial progression should not be used to predict AD progression.

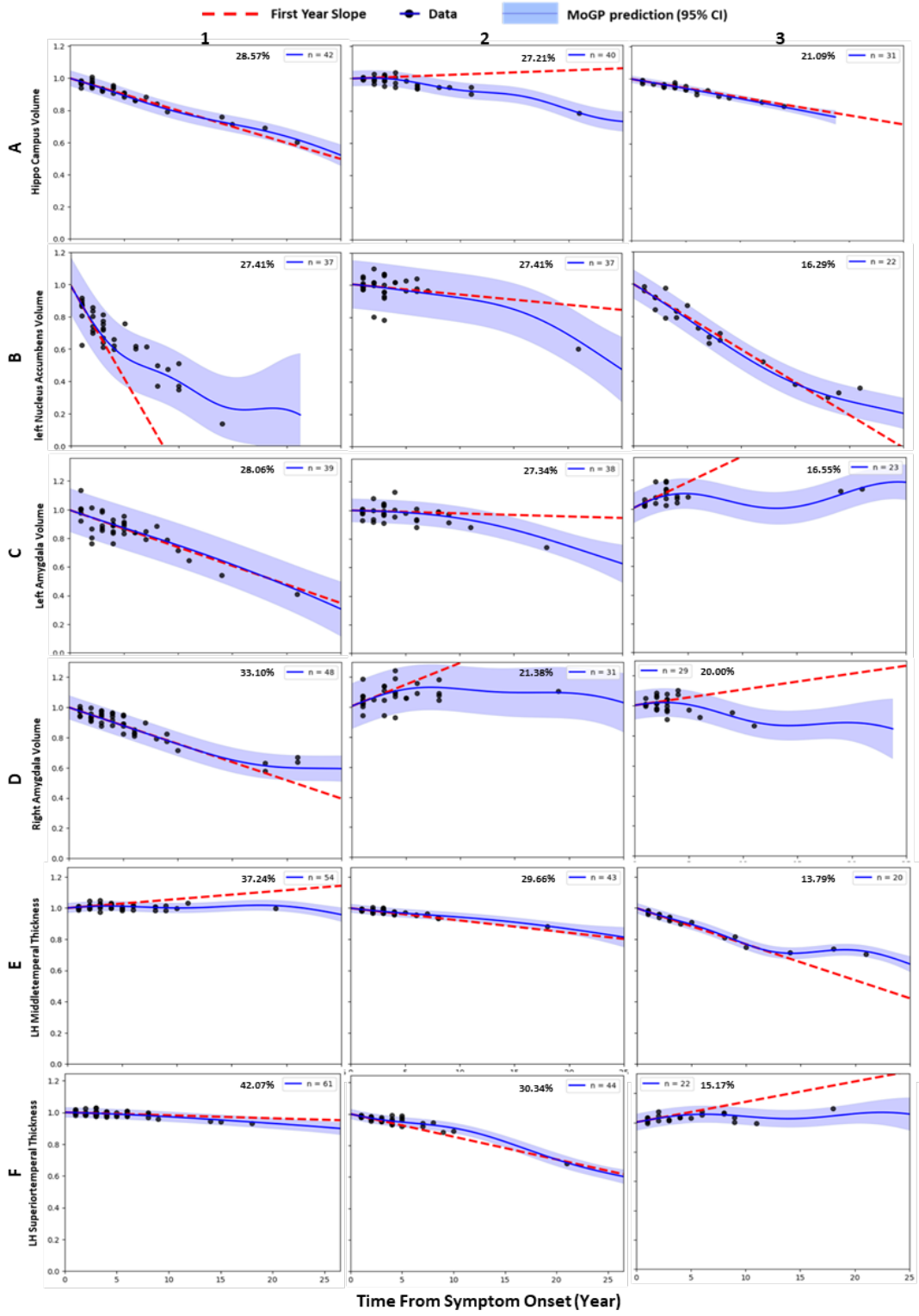

Figure 6. Progression pattern of each biomarker. The number n indicates the number of patients in each cluster. For each biomarker, only the 3 most dominant clusters are demonstrated. L: Left; R: Right; I: Inferior; N: Nucleus; V: Volume; T: Thickness.

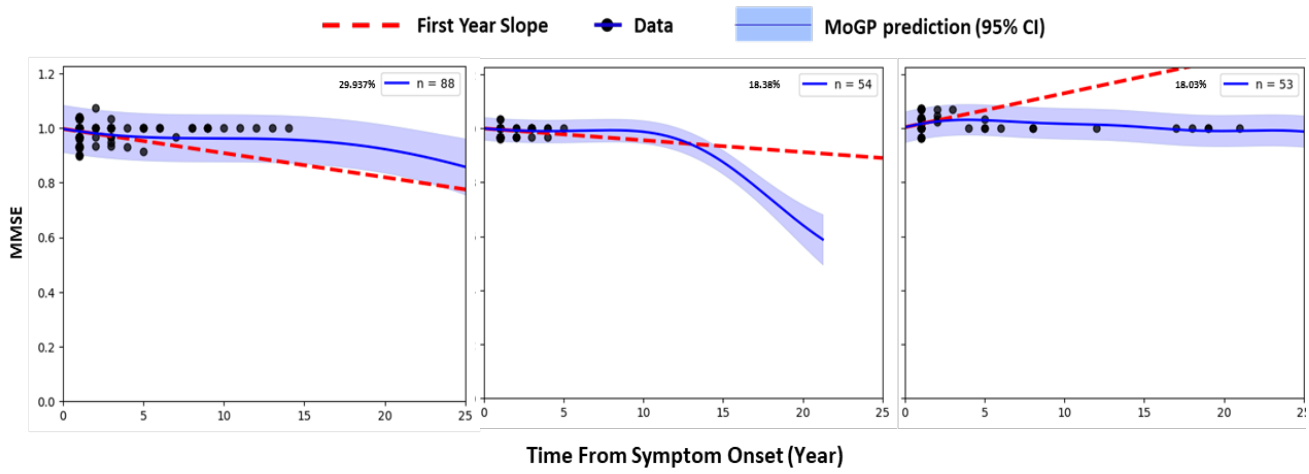

Figure 7. Progression pattern of MMSE with the 3 most dominant clusters are demonstrated. The number n indicates the number of patients in each cluster.

For each biomarker, progression is heterogeneous among the groups of clustered patients in terms of initial progression rate and the progression pattern (Figure 6 and Figure 7). First, the initial progression rate (calculated from $t = 0$ to $t = 1$) varies among the clustered patients (Figure 6). For hippocampus volume, clusters A1 and A3 showed decreasing initial slopes, while cluster A2 has a slight increasing slope for the volume. For Left Nucleus Acumbens, clusters B1 and B3 have a cliff decline in volume, while B2 has a much slower progression rate. Such heterogeneity on initial progression was seen in all other volume and thickness biomarkers as well as MMSE (Figure 7).

Second, the progression trajectory is heterogenous among the clustered patients (Figure 6 and Figure 7). For example, in Figure 6, cluster C1 for the Left Amygdala has almost a quasi-linear decrease in volume, while cluster C2 showed a relatively slow decrease at the earlier years followed by a much faster decline. Finally, cluster C3, showed a sinusoidal pattern. For LH Middle and Superior Temporal, E1, E2, F1, and F3 clusters showed a very slow decline in thickness. The E3 cluster has an S-shape trajectory, and the F2 cluster has a similar trajectory as that of cluster C2. For MMSE score (Figure 7), clusters 1 and 3 have stable values, while cluster 2 has little or no changes in earlier years, but showed a cliff decline in later years.

Heterogeneity was also observed among the biomarkers. In general, LH superior and middle temporal thicknesses (Figure 6 A-D) have more distinct clusters with narrower bands compared to clusters of volume biomarkers (Figure 6 E, F). The progression rate of cortical thicknesses is generally slower than that of volumes. Surprisingly, MMSE does not seem to change significantly as disease progresses, especially the first and third clusters (Figure 7).

Examples of prediction are shown in Figure 8, which shows that the patient data are mostly within the 95% confidence of the assigned cluster, and most RMSE errors are less than 5%, suggesting a good prediction of future progression. The mean RMSE error over all patients in the test dataset is shown in Table 1, which evaluates the general accuracy of clustering.

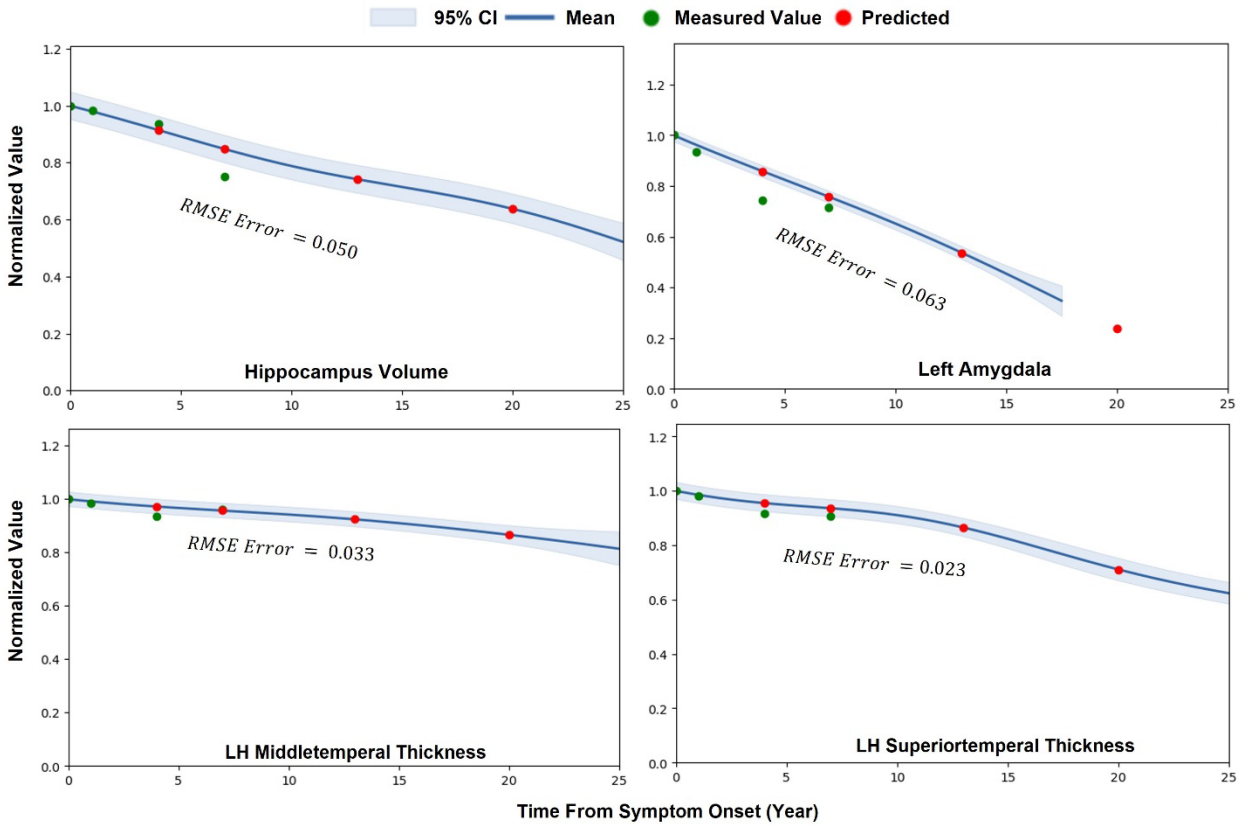

Figure 8. Examples of prediction from clustering.

Discussions

The ability to accurately predict the progression of individual patients would enable personalized data-driven treatment. With the unavoidable environmental and genetic differences, each patient could have a unique progression trajectory with unique risks and responses to therapy. Due to this heterogeneity, current predictive models cannot make individual-level forecasts with high degrees of confidence. The present study used an MoGP model (Fraenkel, 2022; D Ramamoorthy et al., 2022) to characterize AD progression pattern. The model uses Gaussian process regression and Dirichlet process clustering, which are non-parametric methods that do not rely on specific assumptions about linearity or the number of clusters. This allows the model to capture a wide range of nonlinear progression patterns and identify clusters without prior knowledge of the number of clusters.

One of the key novel contributions of this study is clustering the AD progression using both clinical and imaging biomarkers. MMSE (Folstein et al., 1975) and CDR Scale (Khan, 2016) have been widely used to describe the severity and stage of AD. However, the present study showed that MMSE does not have a strong correlation with progression. CDR uses only 5 scales to represent the stage of the disease, and therefore, it is not a good metric to evaluate the progression rare. My previous study showed progression from CN to AD was characterized by increased amyloid deposition, atrophy of the hippocampus, amygdala, and left Accumbens, thinning of left hemisphere temporal, and enlarged inferior lateral ventricles (Song, 2022). Cluster analyses on these biomarkers demonstrated a strong correlation with the progression of AD, particularly in the thickness of the left hemisphere's superior and middle temporal regions. This highlights the significance of examining the morphological changes in the brain that are acquired from MR or PET images. Neither MMSE nor CDR is a reliable indicator of the progression speed of AD.

The results suggested that AD progression is nonlinear and heterogeneous. Nonlinear progression is confirmed by the significant difference between the nonlinear progression trajectory and the initial progression rate (the first-year slope). The heterogeneity is shown in the progression rate among clustered patients and biomarkers. Heterogeneous progression has been reported in several previous studies (Doody et al., 2010; Goyal et al., 2018). However, the results of those studies were based on assumptions of possible progression trajectories, therefore, trajectories that are not included in the assumptions could be overlooked. The difference in progression rate among different biomarkers was also reported by Goyal et al. (Goyal et al., 2018), but the progression path was limited to be from one to another redefined 12 disease stages.

The heterogeneity of progression rates concluded from this study has important implications for the design and interpretation of AD clinical trials. During clinical trials, patients are usually randomly divided into placebo and treatment groups. Inherent heterogeneity or imbalances induced by environmental and genetic differences should be considered while analyzing the differences among the groups so that the effects of the therapy against the placebo can be concluded accurately. The heterogeneous progression rate among different biomarkers of individual patients suggests that multiple types of biomarkers should be analyzed to determine the effectiveness of the treatment method in the clinical trial.

Heterogeneity is also seen in the onset value of each biomarker among patients, which could create a baseline imbalance across the treatment groups. Variations could be due to the patients' genders, age at the time of diagnosis, family medical history, race, education, and many other factors (Song, 2022). Normalizing patient data by their onset value could remove the variations so that the clustering can focus on the progression rate instead of the absolute value of the biomarkers. Previous studies suggested that future clinical trials could benefit from gathering systematic data regarding individual symptom onset, which could be used to estimate the progression and stratify patients by progression group (Doody et al., 2010). However, the present study suggests that the onset value does not correlate with the progression rate. As shown in Figure 4 (A1, B1, and C1), patients with the same onset value fell into different clusters as time progressed. Normalizing the data by onset values results in more distinct clusters (A2, B2, and C2 in Figure 4) and better accuracy (Table 1), suggesting that normalizing the patient's onset value would allow better stratifying patients by progression rate.

Conclusion

The present study used MoGP model to cluster the patients by progression rate. The model enables non-parametric analyses with no assumptions on linearity and number of clusters. it was found that normalizing the biomarker values by each patient's own onset value yielded less overlaps among clusters and resulted in lower errors. The present study also demonstrated that the AD progression rate is nonlinear and heterogeneous. Heterogeneity of progression rate was seen among clustered patients and biomarkers, suggesting the importance of understanding the progression pattern in clinical trials and the treatment.

Limitations

The limitation of the study is the small size of the data, and future studies should apply the same method to a larger size of data to ensure the robustness of the method and the associated conclusions.

Acknowledgments

Data were provided by OASIS-3: Longitudinal Multimodal Neuroimaging: Principal Investigators: T. Benzinger, D. Marcus, J. Morris; NIH P30 AG066444, P50 AG00561, P30 NS09857781, P01 AG026276, P01 AG003991, R01 AG043434, UL1 TR000448, R01 EB009352. AV-45 doses were provided by Avid Radiopharmaceuticals, a wholly

owned subsidiary of Eli Lilly. The MoGP used in current study was modified based on the model developed by Dr. Ernest Fraenkel at https://github.com/fraenkel-lab/mogp.

References

Albert, Y. L. (1984). On a Class of Bayesian Nonparametric Estimates: I. Density Estimates. *The Annals of Statistics*, *12*(1), 351–357. doi: 10.1214/aos/1176346412

Deture, M. A., & Dickson, D. W. (2019). The neuropathological diagnosis of Alzheimer's disease. *Mol. Neurodegeneration*, *14*(32), 1–18. doi: doi.org/10.1186/s13024-019-0333-5

Doody, R. S., Pavlik, V., Massman, P., Rountree, S., Darby, E., & Chan, W. (2010). Predicting progression of Alzheimer's disease. *Alzheimer's Research & Therapy*, *2*(1), 2. doi: 10.1186/alzrt25

Escobar, M. D., & West, M. (1995). Bayesian density estimation and inference using mixtures. *Journal of the American Statistical Association*, *90*(430), 577–588. doi: doi.org/10.2307/2291069

Fisher, C. K., Smith, A. M., & Walsh, J. R. (2019). Machine learning for comprehensive forecasting of Alzheimer's Disease progression. *Sci. Rep.*, *9*(1), 13622. doi: 10.1038/s41598-019-49656-2

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state." *Journal of Psychiatric Research*, *12*(3), 189–198. doi: 10.1016/0022-3956(75)90026-6

Fraenkel, B. (2022). *MoGP: Mixture of Gaussian Processes Model for Sparse Longitudinal Data (https://github.com/fraenkel-lab/mogp)*.

Goyal, D., Tjandra, D., Migrino, R. . Q., Giordani, B., Syed, Z., & Wiens, J. (2018). Characterizing heterogeneity in the progression of Alzheimer's disease using longitudinal clinical and neuroimaging biomarkers. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *10*, 629–637. doi: 10.1016/j.dadm.2018.06.007

Hackeling, G. (2017). *Mastering machine learning with scikit-learn*. Birmingham: Packt.

Jack, C. R., & Holtzman, D. M. (2013). Biomarker Modeling of Alzheimer's Disease. *Neuron*, *80*(6), 1347–1358. doi: 10.1016/j.neuron.2013.12.003

Jack, C. R., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., Shaw, L. M., Vemuri, P., Wiste, H. J., Weigand, S. D., Lesnick, T. G., Pankratz, V. S., Donohue, M. C., & Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *The Lancet Neurology*, *12*(2), 207–216. doi: 10.1016/S1474-4422(12)70291-0

Khan, T. (2016). *Biomarkers in Alzheimer's Disease*. Cambridge: Elsevier Inc.

LaMontagne, P. J., Benzinger, T. L. S., Morris, J. C., Keefe, s., Hornbeck, R., Xiong, C., Grant, E., Hassenstab, J., Moulder, K., Vlassenko, A. G., Raichle, M. E., Cruchaga, C., & Marcus, D. (2019). OASIS-3: Longitudinal Neuroimaging, Clinical, and Cognitive Dataset for Normal Aging and Alzheimer Disease. *MedRxiv*. doi: 10.1101/2019.12.13.19014902

Mehta, D., Jackson, R., Paul, G., Shi, J., & Sabbagh, M. (2017). Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010-2015. *Expert Opinion on Investigational Drugs*, *26*(6), 735–739. doi: 10.1080/13543784.2017.1323868

Meyer, P., Pichet, B. A., Gonneaud, J., Breitner, J., & Villeneuve, S. (2020). Characterization of Alzheimer disease biomarker discrepancies using cerebrospinal fluid phosphorylated tau and AV1451 positron emission tomography. *JMJA Neuro.*, *77*(4), 508–516. doi: 10.1001/jamaneurol.2019.4749

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, *256*(3), 183–194. doi: 10.1111/j.1365-2796.2004.01388.x

Peterson, K., Rudovic, O., Guerrero, R., & Picard, R. W. (2018). Personalized Gaussian Processes for future prediction of Alzheimer's Disease progression. *Arxiv.Org/Abs/1712.00181*. doi: doi.org/10.48550/arXiv.1712.00181

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., & Ferri, C. (2013). The global prevalence of dementia, a systematic review and metaanalysis. *Alzheimers Dement.*, *9*(1), 63–75. doi: doi.org/10.1016/j.jalz.2012.11.007

Ramamoorthy, D, Severson, K., Ghosh, S., Sachs K.; Answer, A. L. S., Glass, J. D., Fournier, C. N., Pooled Resource Open-Access ALS Clinical Trials Consortium, ALS/MND Natural History Consortium, Herrington, T. M., Berry, J. D., Ng, K., & Fraenkel, E. (2022). Identifying patterns in amyotrophic lateral sclerosis progression from sparse longitudinal data. *Nat Comput Sci.*, *2*(9), 605–616. doi: 10.1038/s43588-022-00299-w

Ramamoorthy, Divya, & Fraenkel, E. (2022). Machine learning approach finds nonlinear patterns of neurodegenerative disease progression. *Nature Computational Science*, *2*(9), 565–566. doi: 10.1038/s43588-022-00300-6

Rasmussen, C. E., & Williams, C. K. (2005). *Gaussian Processes for Machine Learning*. Cambridge: MIT Press. doi: doi.org/10.7551/mitpress/3206.001.0001

Rasmussen, C., & Ghahramani, Z. (2001). Infinite Mixtures of Gaussian Process Experts. T. Dietterich, S. Becker, & Z. Ghahramani (Eds.), Advances in Neural Information Processing Systems (Vol. 14). Cambridge: MIT Press.

Silva-Spínola, A., Baldeiras, I., Arrais, J. P., & Santana, I. (2022). The Road to Personalized Medicine in Alzheimer's Disease: The Use of Artificial Intelligence. *Biomedicines*, *10*(2), 315. doi: 10.3390/biomedicines10020315

Song, A. (2022). Using Machine Learning to Forecast Progression from Cognitively Normal to Alzheimer's Disease. *Journal of Student Research*, *12*(2). doi: 10.1101/2019.12.13.19014902

Stern, Y., Liu, X., Albert, M., Brandt, J., Jacobs, D. M., Del Castillo-Castaneda, C., Marder, K., Bell, K., Sano, M., Bylsma, F., Lafleche, G., & Tsai, W. Y. (1996). Application of a growth curve approach to modeling the progression of Alzheimer's disease. *J Gerontol A Biol Sci Med Sci.*, *51*(4), M179–84. doi: 10.1093/gerona/51a.4.m179