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Quantifying the Pathophysiological Timeline of Alzheimer's Disease

Eric Yang*, Michael Farnum, Victor Lobanov, Tim Schultz, Nandini Raghavan, Mahesh N. Samtani, Gerald Novak, Vaibhav Narayan and Allitia DiBernardo and the Alzheimer's Disease Neuroimaging Initiative[1]
Johnson and Johnson, PRDUS

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Abstract. Hypothetical models of AD progression typically relate clinical stages of AD to sequential changes in CSF biomarkers, imaging, and cognition. However, quantifying the continuous trajectories proposed by these models over time is difficult because of the difficulty in relating the dynamics of different biomarkers during a clinical trial that is significantly shorter than the duration of the disease. We seek to show that through proper synchronization, it is possible to de-convolve these trends and quantify the periods of time associated with different pathophysiological changes associated with Alzheimer's disease (AD). We developed a model that replicated the observed progression of ADAS-Cog 13 scores and used this as a more precise estimate of disease-duration and thus pathologic stage. We then synchronized cerebrospinal fluid (CSF) and imaging biomarkers according to our new disease timeline. By de-convolving disease progression via ADAS-Cog 13, we were able to confirm the predictions of previous hypothetical models of disease progression as well as establish concrete timelines for different pathobiological events. Specifically, our work supports a sequential pattern of biomarker changes in AD in which reduction in CSF $A\beta_{42}$ and brain atrophy precede the increases in CSF tau and phospho-tau.

Keywords: clinical trials, disease timeline, progression modeling, synchronization

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease in which alterations in-amyloid-β (Aβ) and tau proteins are implicated in neuronal dysfunction, neuronal death, and eventually in cognitive and functional decline [1]. Characterizing pathogenic events by precise clinical measures, from initial stages through fully developed disease, would be an important step towards understanding disease pathogenesis and developing better markers to detect disease onset and measure progression. Although hypothetical models of disease progression as charted by cerebrospinal fluid (CSF) markers, imaging, and clinical scales have been proposed [1], no studies have quantified the stage-specific and coordinated changes proposed by such models. A major challenge in developing a comprehensive disease-progression model in AD is the long duration of disease [2, 3] compared to the typically short duration of clinical studies [4]. For any given population selected based on similar disease stages within a trial, many pathological changes associated with AD at earlier or later stages of the disease may be missed [5]. Experimental design can mitigate partly against the issue of disease duration by enrolling people at different stages of the disease and following them in parallel, as was done in the Alzheimer's Disease Neu-

[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Authorship_List.pdf.

*Correspondence to: Eric Yang, Tel.: 215-628-7114; E-mail: Eyang3@its.jnj.com.

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roimaging Initiative (ADNI) trial [6]. However, even in well-structured studies like ADNI, the characteristic temporal evolution of specific biomarkers may be obscured by the lack of a synchronized pathophysiological staging framework across clinical stages or even within a given clinical category (e.g., mild AD).

Analyzing biomarker data from subjects at fundamentally different pathologic disease stages introduces a hidden disease-duration covariate that if unaddressed, complicates the task of accurately describing disease progression using biomarkers. A further complication is the fact that different markers of AD pathology appear to change over significantly different time scales and follow nonlinear behavior with respect to time, making it harder to ignore the time axis and draw direct relationships between them. These differential patterns of change may partly account for the lack of a tight correlation between cognitive tests such as ADAS-Cog [7–9], and physiological markers such as CSF $A\beta_{42}$ levels or structural features such as hippocampal volume [10, 11].

Several pathologic stages, with different biomarker signatures, may be present within a given broad clinical category and thereby vex attempts to describe the evolution of typical biomarker changes across clinical categories of disease. To overcome this, we developed a synchronization method that predicts where each subject lies along a calculated timeline of disease progression. From this timeline, we attempted to align a set of well-known proxies for pathology associated with AD, including CSF levels of $A\beta_{42}$, tau, and phophorylated tau (phospho-tau), as well as structural changes in the hippocampus. It has been previously hypothesized that AD pathology consists of a cascade triggered by amyloid accumulation which leads to phosphorylation of tau, neuronal death, and finally cognitive impairment [12]. By doing so, we hope to 1) bring into focus the evolution of these biomarkers; 2) potentially increase our understanding of the interrelations between important pathologic events; and 3) augment our understanding of markers that track disease progression more precisely than data organized by broad clinical staging alone.

METHODS

Data

Data for this manuscript was obtained from the ADNI database (http://www.loni.ucla.edu/) and was downloaded on July 12, 2010. ADNI began in 2003 as a collaboration between the National Institute of Biomedical Engineering and Bioengineering, the Food and Drug Administration, private industry, and various non-profit organizations. The primary goal of this study was to determine the usefulness of various neuropsychological tests, biomarkers, or imaging features for predicting and charting the progression of people with normal cognition compared to those with AD. By understanding the overall progression of the disease as well as the identification of biomarkers, ADNI represents a chance not only to identify relevant targets for therapeutic intervention but also to better design clinical studies with greater power and lower cost. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California San Francisco.

The original goal of ADNI was to recruit 800 participants from the ages of 55 to 90 of which 200 would consist of participants who had normal levels of cognition, 200 patients who were previously diagnosed with AD, and 400 patients who had amnestic mild cognitive impairment (MCI). At the time of the data download, the ADNI trial had enrolled 193 patients with AD, 397 patients with MCI, and 230 participants who were cognitively normal. Of the population of MCI patients, 167 of the patients developed AD over the course of the trial, while 230 patients remained in the MCI category throughout the trial, which at the time of the trial had patient follow-ups for up to 4 years. Among the patients who did not convert during the ADNI trial, it is currently unknown whether these patients will eventually develop AD, another dementia, or will remain MCI.

Model for ADAS-Cog 13 progression and synchronization

ADAS-Cog 13 was selected as the starting point in our synchronization effort because of its wide use, the fact that it is a meaningful measure of disease, and because of the completeness of this measurement in the ADNI trial. The ADAS-Cog 13 serves as the reference clinical measure that we used to synchronize ADNI subjects according to disease severity and, by imputation, their disease stage. The schematic of the overall synchronization process is given in Fig. 1. To generate the appropriate timeline, a model was constructed that used ADAS-Cog scores as an estimate for disease-duration. Because our selection of the ADAS-Cog 13 score was done primarily for pragmatic reasons, other measures of disease severity can be chosen as well.

Various models for ADAS-Cog progression have been proposed, most of which are derived from the

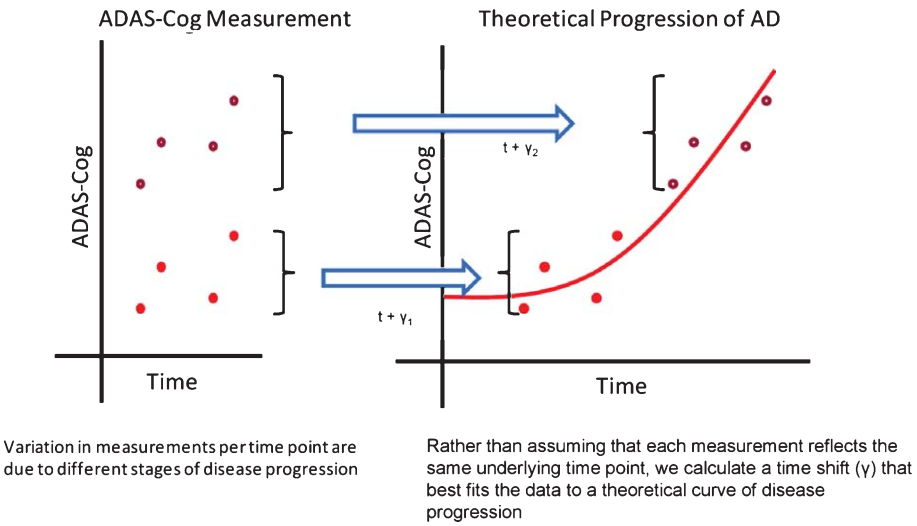

Fig. 1. The overall process of synchronization assumes that the variation observed in the raw data is attributed to the fact that the measurements are taken at different points in the disease progression. Synchronization attempts to line up the different measurements on a theoretical model of disease progression.

basic disease progression model given in Equation 1 [13] where α represents a constant rate of progression, t represents time, and ϵ represents an error term. Such models have been expanded to account for different covariates such as APOE status or age in an attempt to account for some variability in the rate of change in ADAS-Cog scores between different subjects [14].

$$ADAS_{cog}(t) = ADAS_{cog,t=0} + \alpha \times t + \epsilon \quad (1)$$

We opted not to use a linear model, believing that non-linear dynamics better fit the observed progression data. For example Ito et al., found that MCI subjects who later develop AD had lower rates of progression than subjects with AD [15], suggesting that as the disease progresses, the rate of cognitive decline also accelerates. Recent work by Ashford et al. [16] has also suggested that the rate of cognitive decline is nonlinear.

Examination of ADAS-Cog 13 scores for AD subjects in the ADNI cohort is shown in Fig. 2. The data points in Fig. 2 is derived from the progression rate of a subject ADAS-Cog decline versus their average ADAS-Cog score, and the value Φ is the slope of that relationship over the entire population of subjects with AD. Taking the average ADAS-Cog score vs. the regression slope, thus allows us to minimize the effect to noise upon our further calculations. Given the result of plotting the progression rate versus the average score, we can confidently hypothesize that the relationship can be accurately modeled via Equation 2.

$$\frac{dA}{dt} = \Phi \times A \quad (2)$$

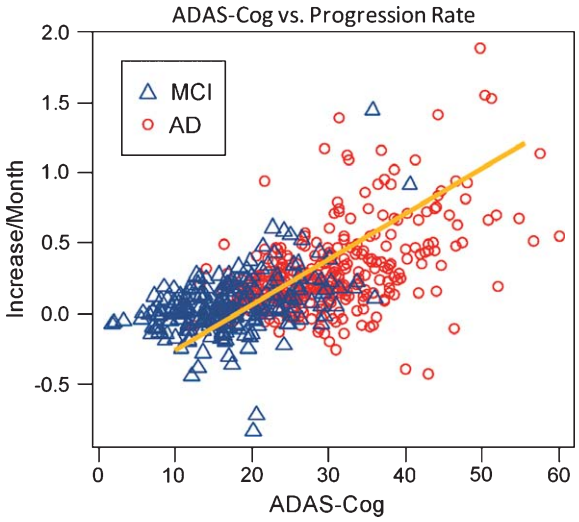

Fig. 2. Plot of d[ADAS-Cog]/month versus ADAS-Cog. The estimated Φ is 0.02.

The analytical solution of Equation 2 is given in Equation 3.

$$A = A_0 e^{\Phi t} \quad (3)$$

In Equation 3, the variable t represents the time from which cognitive decline *starts*. It is important to note that the start of cognitive decline is different from the time at which dementia can be diagnosed. Given the continuous nature of decline, we hypothesize that at AD ($t = 0$), the ADAS-Cog 13 score of a person who is in the process of developing AD will be the same as that

of a cognitively normal person. Thus, A_0 is estimated from the mean ADAS-Cog 13 scores of cognitively normal subjects. To account for the fact that subjects are enrolled in the ADNI trial at different stages of disease progression, Equation 3 is converted to Equation 4.

$$A = A_0 e^{\Phi(t'+\gamma)} \tag{4}$$

For each measurement in the trial, the variable t can be written as $(t' + \gamma)$, where t' represents the time points within the trial (0, 6 months, 12 months, etc.), and γ is a single value that represents the period of cognitive decline prior to a patient's entry into the ADNI trial. We contend that γ, which denotes how long a subject had progressive cognitive decline prior to entering the trial, is the most critical covariate in modeling ADAS-Cog 13 over time. For each subject, the γ parameter is computed by minimizing the difference between the model estimate and the raw data. Solving for a γ parameter is easily accomplished by first log-transforming the raw data, and then converting Equation 4 into a linear equation via the same log-transformation. To calculate γ, it is necessary to minimize the objective function given in Equation 5. The use of this minimization function allows us to compensate for the fact that the standard ADAS-Cog measurement is inherently noisy.

$$\min : \| \ln(A(t')) - [\Phi(t' + \gamma) + \ln(A_0)] \| \tag{5}$$

The γ parameter is then be used to synchronize all other measurements of interest. The overall synchronization procedure is straightforward in that it simply adds the γ parameter for each subject to the time axis of the trial. Thus, each measurement x that is normally given as (t,x) will now be treated as $(t' + \gamma, x)$.

RESULTS

The demographics (age, gender, education, mean Mini-Mental Status Examination (MMSE), mean ADAS-COG) for the subjects utilized in these analyses are provided in Table 1.

Table 1
Demographic Information for the subjects used in the trial

	Males	Females	Average education	Average ADAS-Cog 13	MMSE
Normal	112	102	16.0 ± 2.9	9.3 ± 4.1	29.1 ± 1.0
MCI	149	71	15.7 ± 3.2	17.2 ± 6.0	27.2 ± 1.8
MCI to AD	94	64	15.6 ± 2.9	21.5 ± 5.4	26.7 ± 1.7
AD	96	90	14.7 ± 3.1	28.9 ± 7.6	23.3 ± 2.1

For AD patients, a simple plot of the non-synchronized measurements of ADAS-Cog 13, $A\beta_{42}$, tau, phospho-tau, and hippocampal volume from the UCSD derived volumes are given in Fig. 3. Incorporating patients from other disease stages at this point would only serve to reduce signal-to-noise ratio. In all cases, there is very little apparent change in the measurements over time with respect to sample variability. Previous modeling efforts [15–17] have suggested that additional covariates such as APOE status, cholesterol level, age, etc., can account for some of the variability between patients in their ADAS-Cog scores. Our hypothesis, however, is that the primary source of noise and variability is the lack of disease synchronization between patients. Hence, in our model the primary covariate that must be accounted for is the time from disease manifestation. This covariate, which is not available from the raw data, is calculated in our model as γ.

Applying this calculated variable and synchronizing ADAS-Cog 13 scores, a much more coherent view of disease progression appears, shown in Fig. 4. First, by synchronizing patients via the proposed method, we can easily incorporate subjects at multiple disease stages. Secondly, we can see that the magnitude of biomarker change as a function of disease progression is now much greater than the individual patient variability at a given stage. Based upon the overall time axis, our model suggests that from the time from when cognitive decline starts ($\gamma = 0$) to severe cognitive impairment, the disease progresses over 10 years, which is in agreement with clinical observations [2, 3].

As shown previously in Fig. 3, without calculating and applying γ, it is difficult to precisely characterize the change in the selected CSF biomarker levels or hippocampal volumes over time. However, aligning the measurements by the γ parameter, allows a clearer pattern of change in each biomarker to emerge, show in Figure. As a rough measure of the effect of synchronization, the correlation between the new time axis and individual biomarker measurements are given in Table 2. Given the low correlation between time and biomarker measurements prior to synchronization, it is difficult to suggest that any measure worsens significantly over time. After synchronization, however, the relationship between the different biomarkers and disease progression is more evident. From Table 2 it is also apparent that any change in the analyzed markers over time is small enough to be obscured by the amount of variability introduced by unsynchronized data.

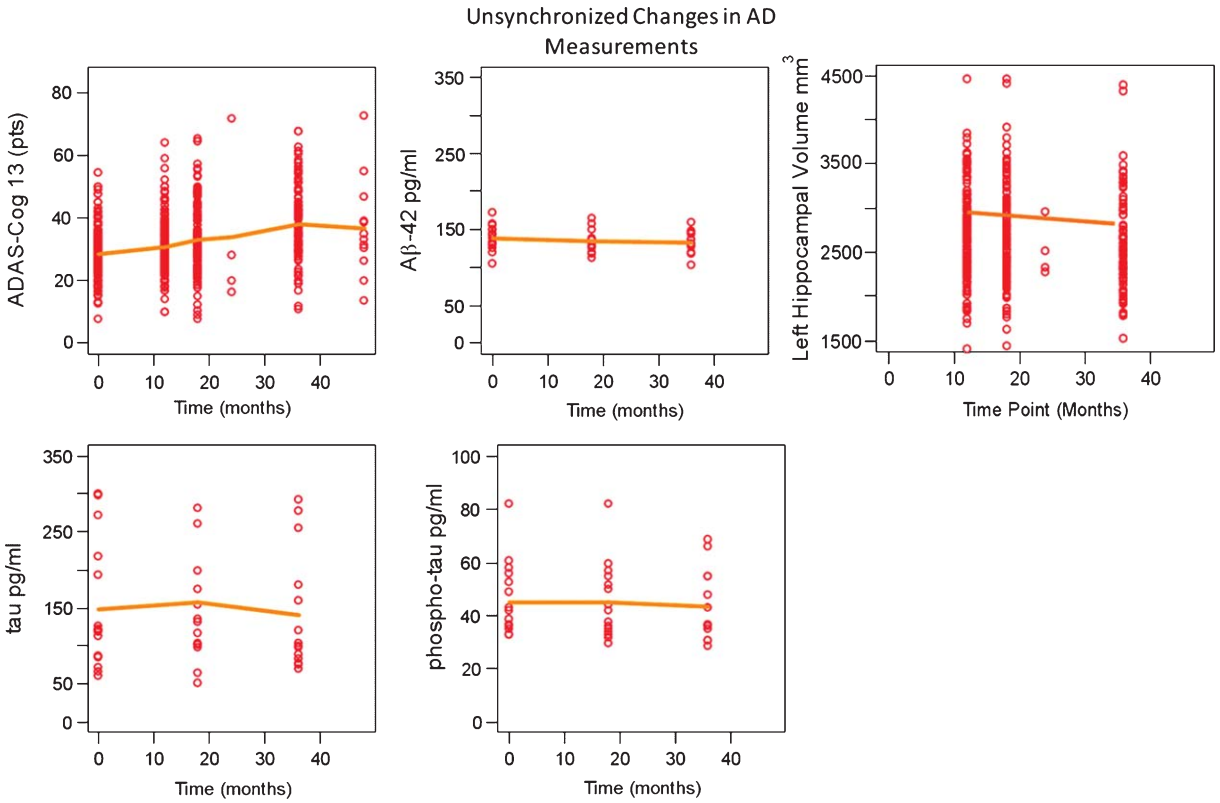

Fig. 3. Measurements of the different clinical endpoints associated with Alzheimer's' disease (AD). In this plot, we have limited the measurements to only those patients who have been diagnosed with AD. In all cases, the variation between the different measurements greatly outweighs the changes of the mean over time. We hypothesize that one of the confounding variables that lead to this is the lack of proper data synchronization. Most of the inherent variability should be reduced after synchronization.

Examining the dynamics more closely, in the case of $A\beta_{42}$, there is an exponential decline that is most rapid during the transition between normal cognition and early cognitive impairment. For tau, there is a sigmoidal increase during the transition between MCI and AD. The levels of phospho-tau display a similar dynamic to that of tau, with the most rapid change occurring during the transition to early cognitive impairment, even while the cognitive changes may be difficult to detect. Finally, for hippocampal volume, we see that during the period before cognitive decline, there is a slow decrease in the overall hippocampal volume, which accelerates upon the initiation of significant cognitive decline. From a diagnostic standpoint, this suggests that the different biomarkers show different levels of sensitivity at each stages of the disease, with $A\beta_{42}$ showing the greatest amount of sensitivity early in the pathologic development of AD, and tau/phospho-tau showing the greatest sensitivity at and around clinical conversion to AD.

DISCUSSION

Our motivation for synchronizing biomarker data according to calculated disease-duration was to improve our description of the evolution of pathologic markers of disease over time. Treating AD as having three different discrete phases (Normal, MCI, AD), it is evident that there is a great deal of overlap and variability in the levels of any biomarkers, and as such it is difficult to determine strict cutoffs in the biomarkers for the purposes of diagnosis. However, by treating the disease as a continuous progress, it becomes possible to place the levels of these biomarkers within the context of disease severity.

We hypothesized that a significant amount of the variability in the data was attributable to imprecise synchronization of disease stage within and between cohorts. By synchronizing data via a calculated γ parameter, we were able to exploit the fact that different stages of disease progression were

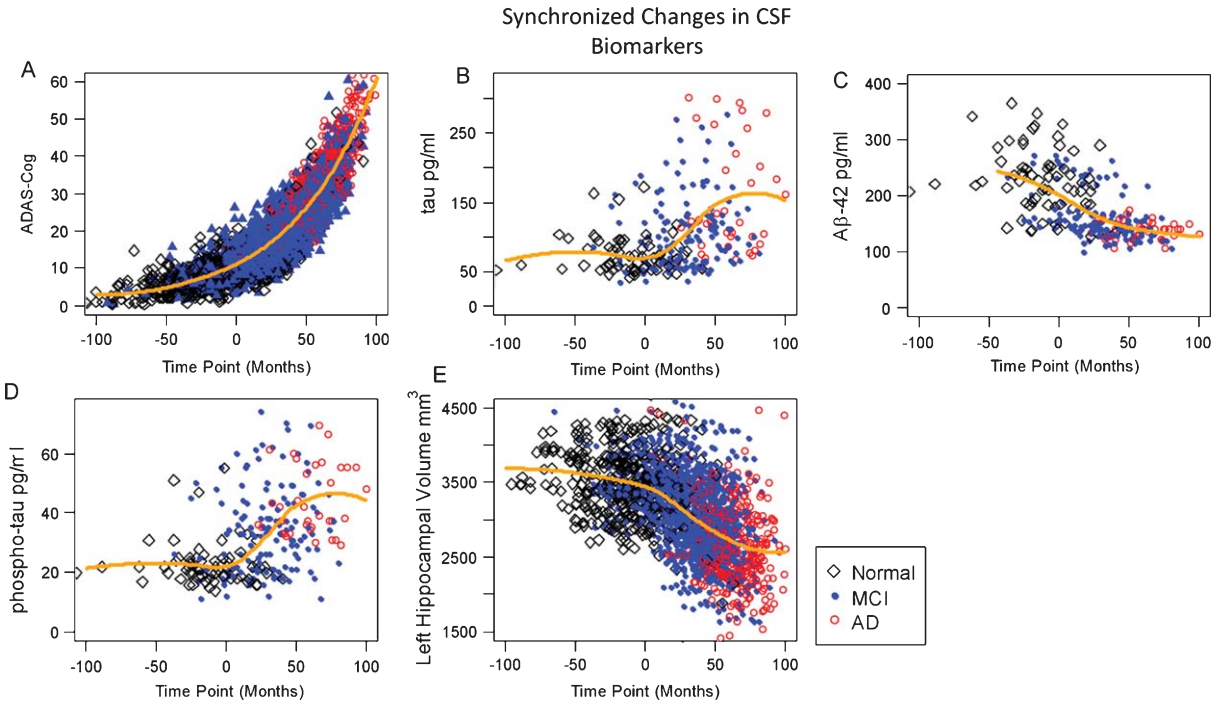

Fig. 4. A) Cognitive Function, CSF biomarkers (B, C, D) and left hippocampal volume (E) after synchronization. Cognitive decline is modeled as an exponential, whereas the rest of the markers are synchronized by γ. B-Amyloid appears to follow an exponential decay whereas tau, phospho-tau, and left hippocampal volume all show some sigmoidal response.

Table 2
Correlation between time and levels of a given pathophysiological measurement. Prior to synchronization, the correlation between biomarker levels and disease duration is weak. After synchronization, however, the correlation is significantly more robust

Biomarker	*R*-Value	*p*-Value
Unsynchronized		
$A\beta_{42}$	–0.15	0.34
Tau	–0.04	0.82
phospho-tau	–0.07	0.68
Hippocampus	–0.00	0.83
Synchronized		
$A\beta_{42}$	–0.58	7.59E-11
Tau	0.47	2.49E-07
phospho-tau	0.58	5.90E-11
Hippocampus	–0.56	7.42E-11

present in the dataset rather than be hampered by it. While we used ADAS-Cog 13 to calculate disease-duration for synchronizing markers in our model, other parameters such as CSF biomarkers or another measures of cognitive decline could serve this function. The only requirement for utilizing another biomarker/measurement is that one must be able to describe a suitable model for the progression of that marker over time.

Applying the γ variable to ADNI data allows the relationship between markers to be seen more clearly than in unsynchronized data. For example, several authors have noted that while CSF $A\beta_{42}$ and tau levels have good diagnostic accuracy [18, 19], there is generally a weak link between the levels of these markers and the amount of current or near-future cognitive impairment in subjects with AD. Our model suggests an alternative pattern that more closely links cognitive function and measureable pathobiologic changes. Importantly, as shown in Fig. 5, the model can potentially describe the association between the level of cognitive functioning and pathologically relevant disease biomarkers throughout the course of disease. In our results, it suggests that Aβ reaches 50% of the saturation point two years before tau/phospho-tau and hippocampal volume reach the same threshold and precedes the same threshold for cognitive decline by more than five years.

It is interesting to note that the biomarker patterns predicted by our model are similar to the hypothetical model proposed by Jack et al. [1], and supports the amyloid cascade hypothesis [20]. In our work as well as the models of AD pathology, $A\beta_{42}$ accumulation, as a triggering event, is reflected early in decreased

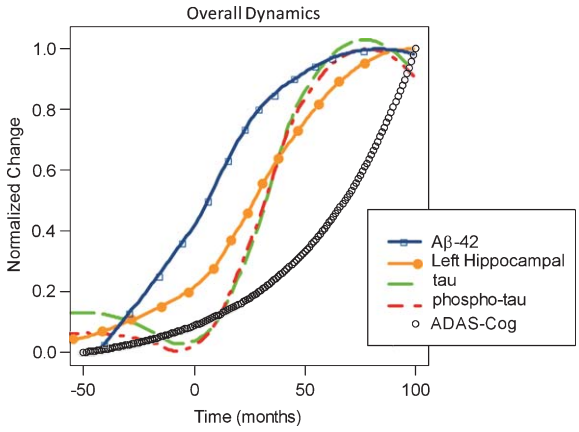

Fig. 5. The overall dynamics of the different CSF Biomarkers. Early on, levels of Aβ decline. As cognition decline around Time 0, Tau/phospho-tau rise abruptly and then level off during the more advanced stages of the disease. Hippocampal Volume shows a modest but steady decline over time, which accelerates when cognition begins to decline. The direction of change for hippocampal volume and Aβ, which typically decline, have been reversed to for easier comparison of their temporal characteristics.

CSF levels of $A\beta_{42}$ prior to cognitive decline, while increased levels of CSF tau and phospho-tau occur around the onset of cognitive decline and closely track with cognitive changes as the disease progresses. Both models also predict that during the period of most rapid cognitive decline, changes in the CSF biomarker levels have essentially leveled off. One key difference is that our results suggest that hippocampal volume changes significantly prior to the onset of cognitive decline, though the decrease in hippocampal volume accelerates when tau levels increase in CSF. This may be due to a combination of changes in hippocampal volume due to aging, as well as due to AD pathology. To our knowledge, this work is the first time the model proposed by Jack et al. has been recapitulated through clinical data, and the time between the pathobiological events detailed in that model has been supported with trial data.

The results suggest that certain biomarkers may be more appropriate at different stages of disease to monitor progression. In particular, hippocampal volume decreases at a modest rate, compared to levels of CSF tau and phospho-tau, which remain relatively stable, when a person destined to develop AD is still cognitively normal. Just prior to the onset of cognitive impairment, the rate of hippocampal atrophy accelerates along with CSF tau, consistent with other reports [21]. Furthermore, when comparing the dynamics of $A\beta_{42}$ compared to tau and phospho-tau in our model, it appears that the latter exhibit the greatest rate of change during the period of rapid cognitive decline, suggesting that cognitive decline is more strongly linked to tau than to $A\beta_{42}$. Thus, although γ was derived originally as a synchronization parameter, its predictions confirm the hypothesized association between tau and cognitive decline [22]. Taken together, these observations demonstrate the ability of subject to improve the resolution of patterns within the data and thereby to potentially extract additional information from biomarker measurements.

We initially considered synchronizing data using concrete events, such as time from clinical diagnosis, but chose to use predicted duration of cognitive decline for synchronization instead. First, we wished to capture subjects who had MCI, but had not been diagnosed with AD. Second, we suspected that relying on clinical diagnoses made outside the ADNI trial could introduce significant variability, and when we had plotted the ADAS-Cog scores versus time of diagnosis in the AD cohort in the ADNI trial, we found that this was the case **Appendix A**. This variability decreased when the diagnosis of AD was undertaken in the controlled environment of the ADNI trial, as seen by the agreement between our disease-duration predictions versus the ADNI clinical diagnosis. For instance, the subjects who take 24 months to convert within the trial, our model predicts a disease-duration of 10 months, whereas those subjects who convert at 12 months had a calculated γ value of 25 months indicating that patients will be diagnosed with AD at roughly the same amount of time after cognitive decline starts.

Given the importance of ADAS-Cog 13 in our model, it is especially important to describe accurately the progression of ADAS-Cog 13 scores in order for the calculation of γ to reflect underlying disease progression. Our model posits a relatively simplistic relationship between the ADAS-Cog 13 score and time without many of the covariates, or utilizing more complex logistic models that account for the ceiling and floor effects intrinsic to the scale. In our initial investigation of the data, shown in Fig. 3, we saw that the relationship between time and ADAS-Cog 13 scores could be easily modeled via a simple first order differential equation. It is striking that the entire progression could be adequately captured through the use of two parameters and one covariate. The small number of variables that must be fitted means that there is ample data to assure that we are not over-fitting the model.

What is more impressive is that the overall amyloid hypothesis seems to be robust despite the fact that we have not considered many complications which may

affect the quality of the model, or the quality of the data fitting. Complications to the analysis that we did not consider include the fact that not all of the patients will have been correctly diagnosed with AD. Though the presence of other dementia such as cerebral vascular dementia or frontal temporal lobe dementia, were considered exclusion criteria, there are a few patients who may have been misclassified. However, in our experience, the number of these misclassifications is relatively few in the AD population for the ADNI trial, and thus have minimal effect upon our overall analysis. Other factors that were unaccounted for, but appear to have minimal effect are the mismatch between the ADNI population versus the general population. We believe that with better diagnosis, as well as understanding as to factors that affect disease progression rate, the results of the analysis can only improve.

Certain covariates that are hypothesized to influence the rate of progression in ADAS-Cog scores have not been included in our model. These covariates either play a lesser role in terms of ADAS-Cog progression than disease duration or may contribute directly to when the disease starts. For instance, covariates like APOE status, which have been utilized by Ito et al., have been linked to the earlier onset of AD, and thus its effect may have been adequately captured by our γ parameter. However, other covariates may affect rate of change, which was something we did not consider, and thus may affect the accuracy of our synchronization variable, which may in turn affect the trajectories of the other biomarkers that we are modeling. Secondly, the lack of the inflection point observed in previous papers examining the ADAS-Cog 11 scores or the MMSE scores [23], may be due perhaps to the greater dynamic range of the ADAS-Cog 13 scores, or the fact that the ADNI trial did not have a large enough cohort of patients who suffered dementia severe enough for the nonlinear ceiling/floor effects to be exhibited in the population. In any case, our simple model does seem to capture adequately the progression of ADAS-Cog 13 scores for our synchronization purposes. However, we suspect that by incorporating relevant covariates, our estimates of γ may be improved.

Further support of the synchronization model is that the estimation of the Φ parameter corresponds well with previously reported values. In our estimation of the parameter Φ in the model, we arrived at a value of 0.02. In the case of a subject who has an ADAS-Cog score of 20, this corresponds to a yearly progression rate of 5·4 points/year, which is in good agreement with prior observations as to the overall progression rate of AD in the first year after diagnosis [15].

CONCLUSION

We used ADAS-Cog 13 to derive a generalized timeline of disease progression onto which we subsequently mapped changes in biomarker data. The creation of this timeline allowed us to better characterize the evolution of small changes in markers of interest of the disease and to better understand patterns of change during the course of disease. We propose that this model could be useful to clarify the relationships between various biomarkers, thereby potentially shedding light on pathologic sequences in AD, linking structural and chemical markers to clinical outcomes like ADAS-Cog or other scales, or by pinpointing optimal biomarkers for specific stages of the disease. In this manuscript, we focused on three well-known CSF biomarkers and one measure of brain morphology, but propose that this model can be easily extended to other biomarkers.

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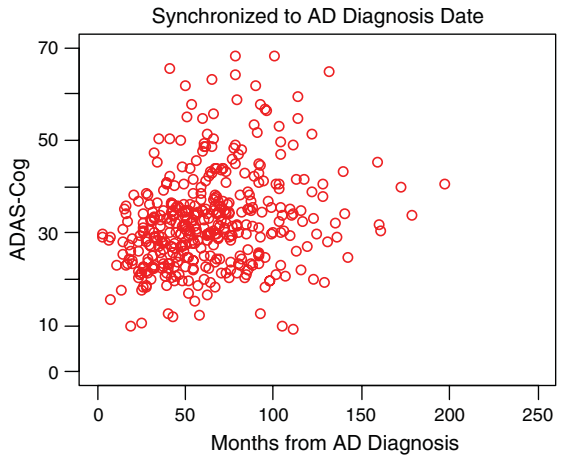
Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=880).

APPENDIX A



Synchronizing patients based upon the number of months from AD Diagnosis do not appreciatively improve the correlation of time versus ADAS-Cog score compared to the non-shifted data, we hypothesized that this was due to the lack of consistency of AD diagnosis in comparison to the ADNI trial.

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