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Preserved Structural Network Organization Mediates Pathology Spread in Alzheimer's Disease Spectrum Despite Loss of White Matter Tract Integrity

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Abstract

Models of Alzheimer's disease (AD) hypothesize stereotyped progression via white matter (WM) fiber connections, most likely via trans-synaptic transmission of toxic proteins along neuronal pathways. An important question in the field is whether and how organization of fiber pathways is affected by disease. It remains unknown whether fibers act as conduits of degenerative pathologies, or if they also degenerate with the gray matter network. This work uses graph theoretic modeling in a longitudinal design to investigate the impact of WM network organization on AD pathology spread. We hypothesize if altered WM network organization mediates disease progression, then a previously published network diffusion model will yield higher prediction accuracy using subject-specific connectomes in place of a healthy template connectome. Neuroimaging data in 124 subjects from ADNI were assessed. Graph topology metrics show preserved network organization in patients compared to controls. Using a published diffusion model, we further probe the effect of network alterations on degeneration spread in AD. We show that choice of connectome does not significantly impact the model's predictive ability. These results suggest that, despite measurable changes in integrity of specific fiber tracts, WM network organization in AD is preserved. Further, there is no difference in the mediation of putative pathology spread between healthy and AD-impaired networks. This conclusion is somewhat at variance with previous results, which report global topological disturbances in AD. Our data indicates the combined effect of edge thresholding, binarization, and inclusion of subcortical regions to network graphs may be responsible for previously reported effects.

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SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <http://dx.doi.org/10.3233/JAD-170798>.

Keywords

Alzheimer's disease; atrophy; biomarkers; diffusion tensor imaging; longitudinal; magnetic resonance imaging; neural networks; structural connectivity

INTRODUCTION

Presence of amyloid- β ($A\beta$) plaques and tau protein-related neurodegeneration are widely accepted biomarkers of Alzheimer's disease (AD) [1–3]. Several proposed models of AD exist, including the $A\beta$ -cascade hypothesis, cascading network failure hypothesis and the prion hypothesis [4]. The current work investigates “prion-like” transmission AD, whereby specific proteins misfold, aggregate, and propagate, causing toxic gain of function and loss of function [5]. It is hypothesized these proteins spread trans-synaptically along neuronal pathways in specific patterns, as observed by classic clinical and anatomical progression in patients [1, 2, 6]. Converging human neuroimaging data showing stereotyped gray matter atrophy and functional connectivity impairments support this view [7–9]. Recently published human neuroimaging of tau protein in AD recapitulate classic disease spread *in vivo*, which further supports trans-synaptic spread hypotheses [10, 11].

The brain's anatomic connectivity, given by white matter (WM) fiber pathways, is thought to play a key role in mediating regional relationships between various imaging biomarkers [12]. Anatomic connectivity appears to be impaired in AD and conversely, might serve as conduit for progressing pathologies [13–16]. Recently, our group proposed a graph theoretic model of tau pathology spread enacted on diffusion tensor imaging (DTI)-based WM connectivity networks. This model, called the network diffusion model (NDM), predicted that observed spatial patterns of degenerative diseases might be explained simply as a consequence of network spread. Subsequently, the NDM successfully predicted future atrophy patterns of AD subjects using their baseline regional atrophy [17]. Thus, the NDM is based on the transmission of tau, but successfully predicts progression of regional atrophy, owing to the strong association between the two [18–21]. In these models, connectivity networks were obtained from healthy subjects only, under the assumption that anatomic connectivity serves merely as a conduit for the transmission and ramification of pathologic entities, rather than itself being the primary target of those pathologies.

It is therefore emerging that both pathology and connectivity affect each other. While highly connected hub-like regions appear to have impaired connectivity in AD, they are also facilitators of pathology, and anchor epicenters or attractors into which pathology accumulates, as given by the network diffusion theory [16, 22, 23]. Intuitively, these hubs receive more exposure to pathogens due to their central roles in the network. Hence it is of interest to determine the causality of these processes, i.e., whether network organization governs disease transmission, or vice versa. Would lower connectivity or deteriorated microstructure impede synaptic spread? Alternatively, would higher pathology burden cause greater impairment of fiber tracts to pathogens and thus augment pathology propagation?

The current study uses network modeling in a multimodal dataset of 124 subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to investigate the impact of AD

pathology on WM network organization, and the impact of WM network organization on pathology spread in the AD spectrum. We hypothesize that if WM network topology is altered prominently in AD, then it would lead to measurable change in the pattern of atrophy spread predicted by the NDM [16]. To test this, we investigate 1) global and local WM network organization changes in AD; 2) the impact of thresholding on network metrics; and 3) NDM performance on both canonical healthy connectomes as well as subject-specific connectomes against empirical regional longitudinal patterns.

MATERIALS AND METHODS

Participants

All subject data were obtained from the ADNI database (<http://adni.loni.usc.edu/>). ADNI is a public-private, large multisite longitudinal study with the goal of tracking AD biomarkers and accelerate prevention and treatment of the disease. Subjects were diagnosed and grouped to AD, late mild cognitive impairment (LMCI), early mild cognitive impairment (EMCI), and Control (CON) according to ADNI data description. 124 subjects were included in the current study. Subjects were included only if they had a WM connectome obtained from a diffusion MRI scan in addition to longitudinal MRI data, which consists of at least one follow-up MRI scan after the baseline MRI scan. The total number of subjects included in the current study are comparable to the number of subjects examined in prior ADNI studies examining structural topology: Prescott et al. [41] ($n = 102$), Daianu et al. [40] ($n = 111$), Daianu et al. [42] ($n = 202$). There were no converters between scans. All subjects meeting these neuroimaging data requirements were included without regard for A β status. All subject groups contained a mix of both A β positive and A β negative subjects. Subject demographic data, including A β group statistics, are depicted in Table 1.

MR image acquisition

DTI and inversion-recovery spoiled gradient recalled (IR-SPGR) T1-weighted imaging data were acquired on several General Electric 3T scanners using scanner specific protocols. Briefly, DTI data were acquired with a voxel size of $1.37^2 \times 2.70 \text{ mm}^3$, 41 diffusion gradients and a b-value of 1000 s/mm^2 . IR-SPGR data were acquired with a voxel size of $1.02^2 \times 1.20 \text{ mm}^3$. All imaging protocols and preprocessing procedures are available on the ADNI website (<http://adni.loni.usc.edu/methods/>).

Image processing

Automated cortical and subcortical volume measures were performed with FreeSurfer software package, version 5.3 (<http://surfer.nmr.mgh.harvard.edu/fswiki>) [24, 25]. For details on T1-weighted data preprocessing, please see the Supplementary Material. Raw diffusion-weighted images (DWIs) were corrected for image artifacts including Eddy current, motion, and EPI distortions using FSL toolbox (<https://fsl.fmrib.ox.ac.uk/fsl>). Diffusion tensors were modeled at each voxel in the brain from the corrected DWI scans using CAMINO toolbox (<http://www.camino.org.uk>). Afterward, the deterministic simple whole WM streamlining was applied on the DTI using CAMINO software. The tissue masks from T1 image was rigidly registered to the first frame of the DWI and used in the deterministic WM tractography. Subject-specific FreeSurfer (Desikan-Killarny) cortical

and subcortical parcellations mapped in the DTI subject space was used to calculate the 86×86 ROI-ROI connectivity matrix.

Network construction and analysis

The number of resulting streamlines connecting any two gray matter regions, including from both cortical and subcortical regions were considered as edge weights in the resulting graphs. To control for inter-subject variance in total streamline count, connectivity density matrices were computed by normalizing streamline count connectomes by the total number of streamlines in each individual.

Characteristic graph metrics to examine differences in network topology were calculated from undirected, weighted structural connectivity matrices. Matrices were not thresholded unless otherwise noted. Network metrics including density, global efficiency, clustering coefficient, local connection strength, local efficiency, and local modularity were computed in MATLAB using the Brain Connectivity Toolbox [26].

Network diffusion model

The NDM is used as described in the Experimental Procedures section of Raj et al. 2012 [16]. The NDM was constructed and illustrated as described in Fig. 1. Briefly, AD-related disease pattern, given by the vector $x(t)$, is modeled as a diffusive process:

$$x(t) = e^{-\beta H t} x_0, \quad (1)$$

where x_0 is the initial regional pattern of the disease, on which the term $e^{-\beta H t}$ acts as a spatial and temporal blurring operator. We therefore call $e^{-\beta H t}$, “the diffusion kernel.” The computation of the above equation is accomplished via the eigenvalue decomposition $H = U \Lambda U^\dagger$, where $U = [u_1 \dots u_N]$, giving:

$$x(t) = U e^{-\Lambda \beta t} U^\dagger x_0 = \sum_{i=1}^N \left(e^{-\beta \lambda_i t} u_i^\dagger x_0 \right) u_i \quad (2)$$

In other words, the NDM is evaluated via the eigen-decomposition of the Laplacian matrix, such that the pattern of disease at any point of time is given as a linear superposition of the eigenmodes u_i 's of the Laplacian. Eigenmodes are calculated using spectral graph theory on the WM 86×86 ROI Laplacian matrix based on spectral graph theory. These eigenmodes, in turn, represent fundamental substrates upon which network spread of pathological entities is enacted.

We modeled each subject's predicted future pathology from the subject's own baseline scan as X_0 in a diffusive process governed by H , which was obtained by either a template control connectome or each subject's own WM connectome. The beta parameter, indicative of speed of pathology spread, was the same for all subjects as well as the time range assessed. Subsequently, the subject's predicted future atrophy at each node was compared to the subject's actual end-state atrophy at each node using correlation analysis. Hence, we

investigated whether the prominent eigen-modes are conserved between patients' individual subject-specific connectomes and a canonical healthy connectome by testing model performance using the template connectome as well as the subject-specific connectome.

Statistical analysis

A cross-sectional design is used to evaluate topology differences in connectomes, because most subjects had a single DTI scan. Independent, two-sided *t*-tests were used to test for differences in characteristic graph metrics between each patient group (AD, LMCI, EMCI) compared to controls. Patient groups were not evaluated in relation to each other. Glass brains depicting magnitude of *t*-statistic using a previously reported method are used for visualization [12, 16, 27]. All reported significant *p*-values survived FDR correction for multiple comparisons and are FDR adjusted unless otherwise noted [28]. In the case of non-Gaussian variables (measured with Anderson-Darling tests), global graph metrics were successfully replicated with non-parametric permutation testing (10,000 permutations) (Supplementary Table 2) [29].

To evaluate changes in connectivity strength in the graph, the Network Based Statistic (NBS) was used. The NBS is a validated, nonparametric statistical method for performing statistical analysis on large networks, which deals with the issue of multiple comparisons by controlling for the family-wise error rate (FWER) [30–32]. FWER-corrected *p*-values are calculated for each component using permutation testing (5,000 permutations). The NBS was used on weighted, non-thresholded networks, with the primary threshold for each link-based *t*-statistic set to 2.5, significantly more conservative than prior studies [33].

Figure 1 illustrates workflow of the NDM. The output of the NDM, $x(t)$, is a vector of positive values at any post-baseline time *t*, representing predicted pathology burden spreading from the baseline regional pattern. Results of the NDM were normalized to a Gaussian distribution via a Box-Cox transformation [34]. Since the NDM by itself is defined in terms of model time and not real time in years, the NDM was executed over a range of 100 arbitrary “model time” timepoints, until the model hit steady state. The NDM always converges to a steady state, which is driven by characteristic eigenmodes, as detailed in a model development paper [16].

Observed pathology, as measured by regional atrophy differences in a subject's longitudinal scan, was logistic rescaled to a value between 0–1 for each subject. To evaluate predictive power of the NDM, we performed whole brain Pearson correlation analysis between predicted pathology versus observed pathology. This analysis was carried out for each of the 100 model timepoints. Since the model is specified in terms of model time, its relationship to a patient's disease duration is not a priori known. Hence we compared empirical subject data with NDM output at all model times, and the model time point that yielded the best correlation was selected. For each subject, correlation analysis was performed to evaluate prediction accuracy of the NDM implemented on the template healthy connectome. Prediction accuracy was also evaluated on the subject-specific connectome. Fisher *r*-to-*z* transformations were used to compare if NDM prediction accuracy changed with connectome choice [35]. All analysis was performed in MATLAB.

RESULTS

Atrophy

First, we confirm whether results from our imaging pipeline reproduce numerous previously published data on this same ADNI cohort. Baseline regional cortical volume from the 86 Freesurfer ROIs are compared between patients on the AD spectrum and controls. Atrophy is corrected for intracranial volume. Figure 2 shows local differences in volume as reflected by *t*-statistics resulting from a two-tailed student's *t*-test, which were obtained at each brain region. All reported regional significance in glass brains survive FDR correction for multiple comparisons. For a full-list of *p*-values see Supplementary Table 1.

Universally, patients show significantly decreased regional cortical volumes (Fig. 2). These data showing prominent atrophy in subcortical and temporal cortices demonstrate that our imaging pipeline reproduces well-known previously reported classic features of AD topography.

Global network analysis

Next, graph theory analysis is used to determine if commonly used metrics of global WM network organization and topology are disrupted in the AD spectrum. Specifically, we assess density, a measure of the overall number and strength of fiber connections, and pathlength, a measure of network integration and efficiency, which is reflective of the ability of the network to sustain information flows [26]. Cortical and subcortical regions constitute the graph. Connectivity matrices are not binarized, but kept as weighted values. Matrices are not thresholded.

Global metrics of density, path length, and efficiency are compared between each patient group and controls. Remarkably, no global metrics are significantly different between patients and controls (Fig. 3). Across all three groups in the AD spectrum, patients show no significant difference in density compared to control subjects (AD: $p = 0.65$, LMCI: $p = 0.65$, EMCI: $p = 0.89$). Similarly, no significant difference is observed in pathlength in patients versus controls (AD: $p = 0.85$, LMCI: $p = 0.65$, EMCI: $p = 0.65$) nor global efficiency (AD: $p = 0.97$, LMCI: $p = 0.82$, EMCI: $p = 0.65$). All reported *p*-values are FDR corrected for multiple corrections. Due to limited sample sizes and the possibility of the summary network metrics being non-Gaussian, we performed a supplementary analysis to confirm the above findings. First, we used the Anderson-Darling test to test for Gaussianity of each metric. Then we performed non-parametric permutation testing (10,000 permutations) for the few variables with non-Gaussian distributions (Supplementary Table 2). In confirmation of above findings, no significant differences were found between groups. Considering all global graph metrics in our cohort, it is clear that the disease groups do not show significantly altered global topological properties compared to healthy controls when weighted, non-thresholded connectivity matrices consisting of both cortical and subcortical regions are used.

Local network analysis

Next, local network analysis is performed to probe distributed topological changes among specific brain regions. We examine local betweenness centrality, a measure of hub-ness, local strength, the sum of a region's connections, and local efficiency, which is a measure of local information flow [26].

Only a handful of nodal differences, concentrated in frontal and temporal regions of all local graph metrics, are observed. However, virtually none of the differences survive FDR correction for multiple comparisons (Fig. 4). In the AD versus CON group, only nodal strength of the left precuneus ($p = 6.66\text{E-}05$) survives FDR correction for multiple comparisons (Fig. 4B). No local metrics in the LMCI versus CON nor EMCI versus CON group survive FDR correction (LMCI and EMCI glass brains data not shown.) Therefore, we show local graph metrics are also not significantly altered between disease groups and healthy controls using weighted, non-thresholded connectivity matrices.

Tract level results

Due to prior reports of significant alterations of graph theory metrics in AD compared to control subjects, we next evaluate the possibility that our tractography and network extraction pipeline is uniquely insensitive to changes in connectivity compared to previous tract-level analyses. Thus, we assess whether the connectivity changes detected by the present methodology agreed with specific tracts reported to be disrupted in AD. To evaluate tract-level changes in fiber strength, we examine strength between every pair of GM regions in the brain (as opposed to previously, a node's sum of strengths), using the NBS as detailed in the Methods.

Significant alterations in a number of WM connections in ROIs along the uncinate fasciculus, superior longitudinal fasciculus, and cingulum bundle (Fig. 5, Table 2). Thus, in agreement with previous literature, connectivity values returned by our pipeline show significant impairment in tract-level WM changes in WM fiber count of AD compared to controls. These results confirm that the non-significant topology findings described above are not due to lack of sensitivity caused by the present study's connectivity and tractography pipelines.

Effect of thresholding

Next, we explore whether our graph metrics appear different from previous reports due to the effect of stringent thresholding and/or binarization. To test whether these effects are responsible for observed discrepancies, we replicate previous findings by thresholding and binarizing our connectomes. Thresholding percentages are defined against raw non-zero connections.

Figure 6 shows thresholding in combination with binarization at a wide range of thresholds k , yields significant results across global metrics of density, path length and global efficiency in AD versus CON (Supplementary Table 3). Specifically, density of thresholded and binarized networks yields significance in the range of $k = 5\text{--}65\%$ (Fig. 6A1), pathlength in the range $15\text{--}60\%$ (Fig. 6A2) and global efficiency in the range $5\text{--}65\%$ (Fig. 6A3).

Thresholding-only of weighted matrices (with no binarization) yields significant differences in topology for a narrow range of threshold K , which include 5%, 30%, and 35% (Fig. 6B2). Similarly, global efficiency is significantly lower in AD than controls at $k = 5\%$ and $k = 10\%$ (Fig. 6B3) (Supplementary Table 3).

Eigenmodes

Our prior work presents the concept of, eigen-modes, “persistent modes”, which is a topological (and linear) metric of the WM connectome governing disease spread. Eigenmodes were shown to form an effective basis on which baseline atrophy data can be projected for prediction of a subject’s future atrophy [16]. We hypothesize that if the network architecture is significantly impacted by AD, as differences in tract-level changes might suggest, then the resulting eigenmodes of the diseased network will be significantly different than those in controls.

To compare eigenmodes between groups, the dot product of eigenmode from the average AD connectome is calculated in respect to that of healthy controls. Since eigenmodes are unchanged by overall sign, the absolute value of the dot product is taken. A value of 1 denotes perfect match between the eigenmodes from the two groups, and a value of zero denotes that the eigenmodes are orthogonal, hence fully dissimilar. The first three eigenmodes are presented as previous studies show the first three eigenmodes are the most stable [16, 36].

We show all eigenmodes dot products are very close to 1, illustrating nearly identical eigenmodes in dementia compared to age-controlled healthy brains (Table 3). Figure 7 presents a depiction of AD and CON network eigenmodes. Thus, despite widespread atrophy and impaired tract-level connectivity, we observe overall architecture of the diseased network does not result in measurable changes to its characteristic eigenmodes.

Performance of diseased connectomes in the network diffusion model

Given no observable AD-related differences in network organization, we examine whether models of AD progression based on WM graph topology is altered in disease. To test this, we use a NDM of pathology spread shown to provide a strong prediction of regional patterns of disease progression [16, 17]. Previously, the NDM was implemented using a healthy template connectome. The current work directly compares performance of the NDM on an age-matched connectome from ADNI controls versus a patient’s own disease-impaired connectome. We hypothesize that if overall network architecture is significantly altered in AD, then the model will give dissimilar outcomes of pathology spread.

The NDM obtains predictions of future regional patterns of atrophy ($x(t)$) from a patient’s baseline volumetric scan (X_0) (Equation 1- Methods). To test model performance, we correlate the subject’s observed end atrophy from a longitudinal scan versus predicted atrophy as modeled by the NDM (See Methods). This procedure was carried out independently on both the healthy template connectome in addition to the subject-specific connectome. The furthest time point with the highest proportion of patients within each patient group was selected to allow for measurement of maximum disease progression.

Figure 8 shows that use of the diseased connectome in the NDM does not significantly increase nor decrease the high correlation between predicted future atrophy and observed end state atrophy. Specifically, Fig. 8A1 shows overall NDM performance on the control connectome, which is obtained by correlation analysis of each subject's predicted future atrophy versus observed end state atrophy.

Because baseline regional atrophy has been shown to highly correlate to future atrophy patterns, the degree to which the NDM improves over baseline is examined. NDM improvement is represented by the change in correlation coefficient (r) between modeled-predicted atrophy versus end state atrophy and baseline versus end state atrophy (Equation 3).

$$\text{NDM Improvement} = \text{Model Correlation to End State} - \text{Baseline Correlation to End State} \quad (3)$$

For example, in AD patients, on average, the NDM yields a model accuracy of $r = 0.80$ between predicted atrophy versus observed end state atrophy. The correlation between baseline regional atrophy versus observed end state atrophy is $r = 0.70$. Thus, the NDM offers improvement of $r = 0.10$, on average, compared to solely using baseline atrophy as a predictor of future atrophy.

Figure 8B1 and 8B2 show each subject's NDM improvement from baseline on both the ADNI control connectome versus a patient's own disease-impaired connectome. Choice of connectome does not appear to significantly impact model improvement. This is confirmed by intra-subject Fisher r -to- z transformations comparing the correlation coefficients (Supplementary Table 4). Furthermore, paired t -tests reveal no significant difference in the time it takes for NDM model to achieve optimal diffusion on control versus individual connectomes (AD: $p = 0.27$, LMCI: $p = 0.22$, EMCI $p = 0.42$). Moreover, analysis in 28 A β -negative subjects show similar results. Fisher r -to- z transformations in A β -negative subjects reveals NDM prediction accuracy does not significantly change with connectome choice (Supplementary Figure 4). This result suggests that A β status is not a differentiator of the ability of the connectome to mediate disease transmission. Please note, this does not mean that A β status does not regulate disease transmission, merely that it does not make the individual connectome more or less useful in predicting longitudinal changes. Thus, taken together, our results suggest that even if certain elements of the WM connectivity network are impaired by disease, they do not impair the overall network organization and topology to the extent necessary to alter the network mediation of AD pathology progression in the AD spectrum.

DISCUSSION

The present study uses network modeling to show that, despite measurable changes in integrity of specific fiber tracts, the overall topological organization of the WM network is not appreciably impaired. Most interestingly, AD does not appear to alter the ability of the network to mediate pathology spread in AD. This conclusion is supported by three main findings: 1) WM network organization, as reflected by graph analysis weighted,

nonthresholded graphs, is largely unchanged between patients and controls, 2) eigenmode analysis confirms no measurable effect of disease on overall network topology, and 3) use of a patient's diseased connectome in place of a healthy connectome does not improve performance of a previously published NDM.

Atrophy in the AD spectrum

First, we confirm the current imaging pipeline reproduces previously reported classic features of AD topography. Specifically, gray matter volume is decreased in AD, globally and especially in subcortical and temporal regions (Fig. 2). This finding is in agreement with published literature [7, 8, 37–39].

Global and local topology

WM disruptions are analyzed using global and local graph metrics. We show topology is not significantly different in all three patient groups compared to controls (Fig. 3). Nodal results converge with global findings. Upon first survey, there are a few nodal differences between patients and controls predominately in frontal and temporal regions. These differences do not survive FDR correction (Fig. 4). However, prior publications report significant changes in network topology in AD versus CON [22, 40–43].

Thus, we next explore the potential causes underlying the discrepancy. We consider two possibilities: 1) Our pipelines for image processing, tractography, and network extraction algorithms are different from previous work, and might be uniquely insensitive to measure changes in connectivity that are known to be present from well-established tract-level analyses or 2) The discrepancy is caused by lack of binarization or thresholding to our connectomes, dissimilar to methodology in previous reports.

Tract-level results

First, we consider the possibility that our connectivity pipelines are insensitive to changes in tract integrity. We assess whether connectivity changes detected by the present methodology comport with specific tracts known to be disrupted in AD. In agreement with previous literature, tract-level changes are detected in WM fiber count of AD compared to controls. We show significant alterations in a number of WM connections in ROIs along the uncinate fasciculus, superior longitudinal fasciculus, and cingulum bundle (Fig. 5, Table 2). These tract-level results of fiber count in AD converge with prior diffusion MRI studies reflective of tract-integrity within the ADNI dataset [44–46]. Taken together, our results and published findings from the ADNI dataset replicate other FA alterations reported in AD as a whole [15, 47–49].

These results confirm preserved global topology findings described above are not due to lack of sensitivity caused by the present study's connectivity and tractography pipelines. Hence, the current work suggests that tract-level alterations in AD do not lead to significant changes in global measures of WM network organization.

Effect of thresholding

Prior work relies on binarization and/or thresholding of connectivity matrices prior to computing graph metrics (Table 4). Hence, we consider the possibility that discrepancy in our graph theory findings is caused by lack of binarization or thresholding being initially applied to connectomes. As previously reported, thresholding these connections can therefore lead to induced topology, an aspect of current graph theoretic approaches that we wished to avoid [50, 51].

When graph analyses are repeated under varying thresholds, followed by binarization, we demonstrate significant results across all three of our global graph metrics at a wide range of thresholds from 5% to 65% of all non-zero connections in the original weighted matrix (Fig. 6A, Supplementary Table 2). Thresholding of weighted matrices with no binarization also yields significant results across all three of our global graph metrics, but at much narrower range of thresholds (Fig. 6B, Supplementary Table 2). These results suggest that thresholding and binarization introduce topological constraints that may be most likely responsible for the apparent contradiction between our data and prior reports of significant topological differences in AD. For instance, many recent reports of topological differences using graph theory within the ADNI dataset found significance after thresholding connectivity matrices based on the k-core “structural backbone” of network hubs [40, 42, 43]. Even this k-core analysis concludes that overall organization of the high-cost and high-capacity networks are relatively preserved in the AD spectrum, a finding which is in line with our results [42]. These results are supported by results in Supplementary Figure 1, which show no significant difference between hub distributions, as reflected by power alpha, in AD versus CON.

The final methodological difference between the current study and prior work is the use of both cortical and subcortical regions in the construction of the network graph. Previous work recognizes that the addition of subcortical regions refines network organization [42]. Few prior studies use graphs consisting of both cortical and subcortical regions (Table 1). Interestingly, prior work using subcortical and sub-cortical regions in addition to no binarization nor thresholding successfully replicate our results of no significant findings of global efficiency or path length in AD [31, 52]. Density is not assessed. Importantly, concerns of diffusion MRI quality or other study-specific bias are mitigated because these studies were replicated in AD cohorts independent of ADNI.

Characteristic eigenmodes

Thus far, the present study had explored global and local graph metrics, which are usually non-linear and sensitive to edge thresholding and binarization, as demonstrated above. Given this strong dependence on somewhat arbitrary parameters, we sought to determine if characteristic eigenmode, a topological (and linear) metric governing disease spread, is altered in dementia. We have previously shown that any network spread process implies a prominent role for the so-called network “eigenmodes”, which were shown to form an effective basis on which atrophy data can be projected for potential differential diagnosis. These eigenmodes are useful predictors of dementia, the spread of epilepsy and of normal brain activity [16, 54]. Furthermore, eigenmodes represent distinct spatial patterns that bear

a strong resemblance to known patterns of various dementias and recapitulate recent findings of dissociated brain networks in dementia [55–58]. Our prior work shows evidence that there is a one-to-one correspondence between the healthy network's eigenmodes and atrophy patterns of normal aging and dementia [16]. The first 2–3 principal network eigenmodes appear to be reproducible between healthy subjects, and the first two eigen-modes appear to be largely conserved even in patients with congenital agenesis of corpus callosum [36].

Interestingly, the current work shows eigenmodes, which are important predictors of degenerative progression, are virtually identical in AD versus CON (Table 3, Fig. 7). This suggests that despite widespread atrophy and clear evidence of impaired tract-level connectivity, characteristic eigenmodes, global network architecture is preserved.

Performance of the network diffusion model

Given no observed significant differences in network architecture in AD versus CON, we examine whether models of disease progression based on WM network topology is altered by disease. To do this, we utilize the NDM, a recent graph model of pathology spread that successfully predicts regional patterns of disease progression [16, 17] (Fig. 1). The previously published model is based on a template healthy connectome, under the assumption that the structural network serves merely as a conduit for transmitting proteinopathies, rather than being the first to be impaired itself.

In the present study, we asked whether the model would give similar outcomes if a patient's own disease-impaired connectome was used in place of a healthy connectome. Thus, by exploring the effect of individualized patient connectomes on the NDM, we sought to determine indirectly whether the overall network architecture is significantly altered by disease, to the extent of causing measurable differences in how pathology might travel on the network.

Use of patient-specific connectomes in place of an age-matched, control connectome does not improve prediction of a patient's future gray matter atrophy (Fig. 8). Personalized individual connectomes perform just as well, but not better, than healthy connectomes in capturing the longitudinal evolution of regional atrophy in AD. This finding is true across all three dementia groups of AD, LMCI, and EMCI. Performance similarity between connectomes does not reflect poor predictive ability of the NDM, which gave typically high correlations ($R > 0.8$ in most cases). To mitigate possible concerns of DTI quality in ADNI, this result was replicated using an average connectome obtained from an independent high resolution DTI dataset of younger control subjects, whose subject demographic and data preprocessing methodology utilized probabilistic tractography and is detailed in [59] (Supplementary Table 2). Equal performance of the NDM between subject-specific diseased and healthy connectomes supports our conclusion that overall WM network organization is preserved in AD, and tract-level impairments do not lead to altered mediation of pathology spread in AD.

The finding that the overall network architecture is preserved in dementia points to the possibility that neurodegenerative pathology primarily targets gray matter rather than the WM network architecture, a finding widely replicated in topological studies of the GM

network [60, 61]. Hence, either WM connectivity alteration is minor in the global brain context, or our measurement techniques are insensitive to pick it up. There is one other possible explanation specific to the NDM results. Connectivity alterations, even if significant, might happen in a manner that does not change the topographic spread patterns the network will sustain. This is supported by the finding that thresholding weighted networks, which we show induces changes in graph metrics, does not result in significant changes to NDM performance (Supplementary Figure 2, Supplementary Table 5). This points to an inherent strength of near-linear models like the NDM: Small changes in network connectivity will only elicit a correspondingly small change in the output of the model. This stands in stark contrast with most current graph theoretic summary metrics like path length and efficiency, which are inherently non-linear. Note that these non-linearities persist even if the metrics are redefined to utilize weighted rather than binary connections, because these metrics are defined with respect to *implied neighbors*, which is essentially a binary decision. This point is helpful in interpreting the threshold dependence widely seen in graph theoretic concepts, and also replicated here in Fig. 6.

We have already noted that overall network topology measured by graph theoretic metrics appears resistant to local changes in fiber integrity. Connectivity loss will, of course, change the speed of network spread according to the NDM model, but appears not to change the latter's predictive ability (maximized over all model times). The speed of network spread, encapsulated in the model parameters β and $t_{\max}$, is a key feature of the NDM, but was not considered here because our focus is on predictive power of future atrophy patterns rather than their timeline. Fitting rate parameter of the NDM, and its neural/genetic correlates, will be the subject of our future work.

Limitations

Technical limitations of the volumetric and tractography processing pipelines include HARDI spatial and angular resolution, coregistration errors, low test-retest reliability of volumetric data, and the distance bias inherent in tractography. Therefore, it must be acknowledged that the atrophy and connectivity results in this paper share the same sensitivity and accuracy issues that are common to all computational neuroanatomic data currently in public domain. However, we note that our connectome technique was able to successfully pick up changes in tract-level connectivity, hence methodological limitations and insensitivity may not be the primary driver of our key results. Global and local graph theory analysis results with respect to the WM connectome were obtained by using deterministic fiber tracking implemented in Camino, and may be different if probabilistic tracking methods were applied. To mitigate concerns of tractography quality and deterministic tractography methods, we illustrated reproducibility of NDM results on probabilistic tractography gathered and processed in an independent control dataset (Supplementary Table 2).

The NDM is a first-order, linear, parsimonious model of diffusive spread that assumes that the structural connectivity network remains static and unchanged over the duration of the longitudinal analysis. This is reasonable because the observation window (2–4 years) is short compared to the course of the disease. Additionally, although the model enables long-term

projections of future atrophy, model validation in the current work is limited to public (ADNI) data sets of rather narrow time span (2–4 years), preventing long-term longitudinal follow-up. This is a future point of work that will be addressed as the ADNI study continues to collect additional longitudinal data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Workflow graphic of the NDM. A subject's baseline gray matter atrophy pattern and white matter connectome are used as inputs to the NDM. (1) The model predicts a subject's future atrophy at a single time point on a 0–1 scale. (2) Model accuracy at a single time point is determined by correlation analysis of predicted end atrophy versus measured end atrophy. Measured end atrophy is determined by a subject's longitudinal scan. (3) The NDM model is modeled over a wide range of time units, until the model hits steady state. The resulting curve is the model's prediction accuracy over a range of model time units. The highest

correlation at any time, which represents the model's best prediction accuracy, is selected as $R_{\max}$. (4) This analysis is carried out for each subject. Each subject's $R_{\max}$ is depicted.

Fig. 2.

Glass brains displaying cortical volume in CON versus AD. Size of the blue sphere represents the magnitude of the regional difference in volume, as reflected by the t-statistic, between AD and age-matched controls. Blue denotes atrophy in AD versus CON. Figure thresholded for significance at $p < 0.05$ and all illustrated results survived FDR multiple corrections. For a full-list of p -values, see Supplementary Table 1.

Fig. 3. Global network measures in the AD spectrum, A) AD B) LMCI and C) EMCI, versus controls. All reported p -values are FDR corrected for multiple comparisons. Results were confirmed via permutation testing (10,000 permutations) in the case of non-Gaussian variables. Bar charts depict the standard t -test.

Fig. 4. Glass brains of local network measures of A) Betweenness Centrality B) Strength and C) Local Efficiency in AD versus CON. Images are thresholded at $p < 0.05$ significance and no reported p -values survived FDR corrections except regional strength in the left precuneus. Blue denotes decreased in AD compared to CON. Green denotes increased in AD compared to CON.

Fig. 5. Glass brains of tract-level differences in AD versus CON as measured by ROI-ROI connectivity strength using the NBS. Blue notes decreased in AD relative to CON.

Fig. 6.

Graphs of global metrics density, pathlength, and efficiency. A) Weighted matrices are binarized and thresholded at various percentages of non-zero connections, as represented by k . B) Weighted matrices are thresholded with no binarization, at various percentages of nonzero connections, as represented by k . *indicates significance between AD and CON. The blue line represents controls and the red line represents AD.

Fig. 7.

Topology of nearly identical eigenmode 1, eigenmode 2, and eigenmode 3 of A) AD connectomes and B) CON connectomes. The size of each sphere is reflective of each region's eigenmode. The bigger the sphere, the larger the eigenmode, or "hubness", of the node in the structural network. Blue denotes positive and yellow denotes negative; note however that eigenmodes are invariant under a global sign change.

Fig. 8.

NDM performance on individual patient connectomes versus age-matched control connectomes. A) NDM on the control connectome, by correlating predicted future atrophy versus measured atrophy. B) Model improvement from baseline on the control connectome. C) Model improvement from baseline on the individual connectome.

Table 1

Demographic information of study participants

Group	n	Age (std)	Age versus CON	Male / Female	Gender versus CON	A β Burden (std)	A β versus CON	%A β ⁺	Time Elapsed From Baseline [*]
AD	19	73.5 (9.9)	$p = 0.64$	11M / 8F	$p = 0.22$	1.45 (0.15)	$p = 5.07\text{e-}13$	100%	131.3 days
LMCI	26	72.6 (6.3)	$p = 0.86$	18M / 8F	$p = 0.50$	1.34 (0.22)	$p = 4.10\text{e-}07$	81%	532.8 days
EMCI	42	70.5 (7.7)	$p = 0.23$	24 M / 18 F	$p = 0.03$	1.19 (0.24)	$p = 0.015$	45%	454.7 days
CON	37	72.4 (6.1)	-	19M/18M	-	1.08 (0.13)	-	27%	-

⁺ Denotes % of subjects A β -positive based on AV45 PET scan with a 1.11 cutoff for positivity.

^{*} Denotes average time elapsed from baseline to final longitudinal scan on which NDM model is tested.

Table 2

Region pairs with decreased ROI-ROI connectivity strength in AD relative to CON as measured using the NBS. Alterations depicted above in Fig. 5

Regions	Tract	Hemisphere
Subnetwork 1, $p = 0.01$		
Isthmus Cingulate / Post Central	CB	Right
Isthmus Cingulate / Precentral	CB	Right
Paracentral / Precentral	SLF	Right
Post Central / Putamen	—	Right
Transverse Temporal / Putamen	UF	Right
Subnetwork 2, $p = 0.01$		
Caudal Anterior Cingulate / Parsopercularis	CB	Left
Paracentral / Parsopercularis	SLF	Left
Caudal Anterior Cingulate / Parstriangularis	CB	Left
Parsopercularis / Posterior Cingulate	CB	Left
Caudal Anterior Cingulate / Rostral Middle Frontal	CB	Left
Caudal Middle Frontal / Rostral Middle Frontal	SLF	Left
Caudal Middle Frontal / Superior Temporal	—	Left

UF, uncinate fasciculus; SLF, superior longitudinal fasciculus; CB, cingulum bundle.

Table 3

Absolute value of dot products of group-wise comparisons of characteristic eigenmodes. A dot product of 1 denotes eigenmode equivalence

Eigenmode	AD • CON	LMCI • CON	EMCI • CON
1	1	1	1
2	0.9986	0.9995	0.9996
3	0.9983	0.9991	0.9986

Table 4

Summary of prior studies involving AD-related topological characteristics. Highlighted studies indicate results replicated by the current study

Study & Patient Group	ADNI	Network Construction	Included Subcortical	D	E _{glob}	L _p	Comments
Current Study MCI & AD	✓	Weighted, Unthresholded	✓	NS	NS	NS	
Lo et al.[22] AD		Weighted, Thresholded		-	▼	▲	
Baiaetal.[31] MCI		Weighted, Varying Thresholds	✓	-	NS	NS	Metrics reported at 0 thresholding
Reijmer et al.[52] MCI & AD		Weighted, Unthresholded	✓	-	NS	NS	
Daianu et al. [40] MCI & AD	✓	Binarized, Varying k-core thresholds		-	▼	▼	Created graphs by hemisphere
Prescott et al.[41] MCI & AD	✓	Weighted, Unthresholded		-	-	-	Grouped metrics by cortical lobe
Daianu et al. [42] MCI & AD	✓	Binarized, Varying k-core thresholds		-	▼	▲	
Daianu et al.[43] Early-On set AD		Binarized, 1 K-Core threshold		-	-	-	Evaluated location of hubs only
Fischer et al.[53] Preclinical AD	✓	Weighted, Thresholded	✓	N/A	N/A	N/A	Subjects not comparable+

D denotes density, E_{glob} denotes global efficiency, and L_p denotes pathlength. ▲ denotes increased in AD versus CON, ▼ denotes decreased in AD versus CON, NS denotes nonsignificant, – denotes metric not assessed in study design, N/A denotes study results not directly comparable to the current study due to subject population. +Preclinical AD versus Control subjects defined in cognitively healthy older adults on basis of global amyloid beta burden only, with preclinical converter status unconfirmed.