Predicting topographic patterns of future atrophy in Alzheimer's disease using network diffusion model

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Target Audience: Clinical neurologists, radiologists and basic scientists interested in neurodegeneration and its pathoclinical progression in the brain.

Purpose: Alzheimer's Disease (AD) is a neurodegenerative dementia whose precise pathophysiological etiology and mechanisms of spread in the brain are largely unknown. Recent studies on prion-like trans-neuronal proteopathy [1] of dementias suggest transmission along fiber pathways of the brain network. Using recently developed mathematical models capturing this spread as a network-diffusion process on the structural (tractography-derived) brain network [2] provides a new and unparalleled window of opportunity to study the exact progression of the disease and as a means of anticipating its future course. Here we apply this model to predict future atrophy of individuals using baseline MRI. To our knowledge this is the first fully quantitative, testable model of macroscopic transmission of degenerative processes in the brain. Our results indicate that the course of disease is deterministic and predicated on the connectivity network of the brain. The model implies that diverse proteopathic etiologies could produce shared spatial patterns, possibly starting from medial temporal origins [3], whose subsequent spread requires neither selective vulnerability nor differential stressor loads [4].

Method: MRI processing: Baseline and end-of-study regional atrophy and its rate of change were obtained using Freesurfer volumetric software applied to longitudinal structural (T1, 1mm isotropic voxels) MRI scans from the ADNI database of 687 age-matched normal, AD and MCI subjects. Connectivity data for the mode was obtained from 14 young normal subjects' structural T1 and diffusion (b = 1000, 30 directions) scans on a 3T GE magnet. Connectome processing followed [2,5]; briefly: 1) T1 and diffusion volumes were co-registered; T1 volumes were parcellated using Freesurfer atlas; these regions seeded DTI tractography; tracts terminating in a pair of regions were probabilistically summed to give the connectivity between them.

Model: At time t, the vector x(t) of atrophy at all nodes in the network is modeled by the dynamics of the "network heat equation" $\frac{d\mathbf{x}(t)}{dt} = -\beta \mathrm{H}\mathbf{x}(t)$ *where* H is the graph Laplacian matrix [2]. Its solution via matrix exponentiation is $\mathbf{x}(t) = e^{-\beta H t}\,\mathbf{x}_0$. This time-evolution equation was applied to the baseline MRI volumetrics and the result was compared with end-of-study atrophy pattern in individuals, using Pearson correlation as performance metric. The analysis is summarized below:

Prediction of future atrophy patterns For each subject:

- Baseline MRI volumetrics = $\boldsymbol{x}_0$
- End-of-study volumetrics = $\boldsymbol{x}^{obs}(t_{end})$
- time-evolution eqn above was applied to get $\boldsymbol{x}^{pred}(t_{end})$, the predicted end-of-study atrophy.
- Slope (atrophy rates) were computed: $\Delta\boldsymbol{x}^{obs}$ and $\Delta\boldsymbol{x}^{pred}$
- $\boldsymbol{x}^{obs}(t_{end})$ and $\boldsymbol{x}^{pred}(t_{end})$ were correlated over all regions

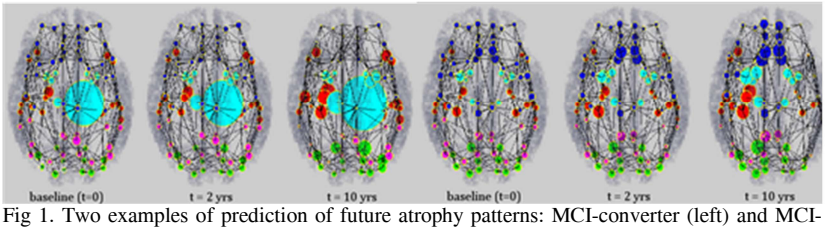

Fig 1. Two examples of prediction of future atrophy patterns: MCI-converter (left) and MCI-non-converter (right). Nodes represent brain structures, color-coded by lobe. The predicted patterns are clearly distinguishable by their AD-like and non-AD-like topography, respectively.

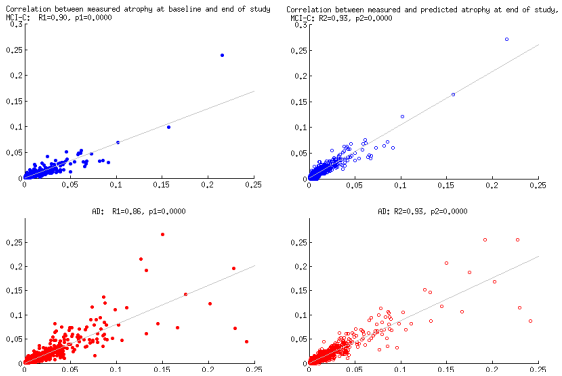

Figure 2. Correlation between baseline and end-of-study atrophy patterns (left), and correlation between model prediction applied to baseline, and end-of-study pattern (right). The model improves the correlation in both the MCI group (top) and AD group (bottom).

Results: First we show examples of the prediction of topographic distribution of atrophy in two individuals – a MCI-converter and a MCI-non-converter. Figure 1 depicts these patterns, visualized as a set of spheres representing brain regions, and size representing the amount of atrophy in that region. Baseline and future predicted patterns are shown. Pearson correlation of measured and predicted atrophy at the end of study was R = 0.93 for both AD and MCI groups. This compares very favorably with the straight correlation between baseline and end of study, which is 0.90 for MCI and 0.86 for AD. As expected, MCI at baseline is already quite close to end of study, due to early stage of these patients. The addition of the network-diffusion model, however, improved the correlation significantly (as measured by Fisher's R to z transform, whose significance values are shown alongside) over the straight correlation (Table and Fig 2).

Discussion: Assuming that Pearson correlation between predicted and measured future topographic atrophy patterns is a reasonable proxy for predictive ability, we conclude that the proposed predictive model stands validated. Our success in demonstrating the topographic prognosis of AD patients using the model lends support to pathophysiological seeded proteopathic transmission mechanisms acting as a diffusion process enacted on the brain's network. This observation opens up new possibilities in interpreting pathophysiological data using quantitative network tools. In particular, these results provide a mechanistic and deterministic explanation of the well-documented dynamics of AD pathology and phenotype [6]. The clinical utility of a quantitative model of dementia progression, like the network-diffusion model, is in its ability to predict future topographic atrophy patterns in individual patients based on their baseline MRI. We demonstrate this here using longitudinal regional atrophy data measured from ADNI database. Successful predictability of future dementia patterns can greatly impact patient care, prognosis and therapy monitoring. If proved reliable and accurate, this model would be particularly useful for both prognostic and clinical trial assessment as it could both predict cognitive decline and quantify treatment-induced deviation from this anticipated decline.

Table 1	No model	Net-diffusion model	Fisher's R to z	P value
MCI	0.90	0.93	1.85	0.032
AD	0.86	0.93	3.62	0.00015

Table: The R value of correlation between end of study and baseline ("no model"), and between end of study and the future prediction from baseline of the network diffusion model.

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