Testing models of neurodegenerative spread via regional atrophy and its slope

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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 with a highly stereotyped tophographic distribution and temporal progression of atrophy patterns in the brain – a pattern that is highly conserved between individual AD patients. Starting from medial temporal origins in the hippocampus and entorhinal cortex, the disease appears to spread along connecting white matter fibers to adjoining temporal cortices, thence to parietal and finally frontal cortex, recapitulating the famous Braak model [1]. The precise pathophysiological etiology and mechanisms behind this stereotyped spread are largely unknown, although several hypotheses have been proposed, including selective vulnerability [2], differential stressor loads [3], and activity-dependent degeneration [4]. Recent studies on prion-like proteopathy [5] are beginning to suggest that trans-neuronal transmission might be a fundamental mechanism behind many degenerative diseases. These descriptive studies were recently turned into a deterministic and quantitative mathematical model of spread along fiber connectivity of the brain, as a network-diffusion process on the structural (tractography-derived) brain network [6]. The **purpose** of this study is to quantitatively compare the above models of degeneration by applying them to MRI-derived volumetric data from the public ADNI database. Specifically, we consider three alterative models: a) non-networked model of activity-dependent degeneration [4], b) non-networked sigmoid model proposed by Jack et al [7], and c) the network-centric diffusion model [6]. We test these models on how well they capture the relationship between baseline and rate of change of atrophy in the ADNI dataset. To do this, we first show that each model predicts a distinct and testable relationship between atrophy and its rate of change, which, as depicted in Fig 1, is time- and disease stage-dependent. Different regions of the same brain may be at different stages of the curve and this relationship ought to be captured by each model.

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 [6]; briefly: 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 $\mathbf{x}(t)$ of atrophy at all nodes in the network is modeled by the dynamics of 3 alternate models:

a) Activity-dependent degeneration: this is an exponential model, since the rate of degeneration depends on its current level: $\frac{d\mathbf{x}(t)}{dt} = \alpha\mathbf{x}(t)$, which gives $\mathbf{x}(t) = e^{\alpha t}\,\mathbf{x}_0$.

b) Sigmoid model: Since a) would either monotonically rise or fall, we use a sigmoid instead of exponential model, as suggested by Jack et al [7]. For a sigmoid of the form $\mathbf{x}(t) = 1/(1+e^{-\gamma t})\mathbf{x_0}$, we have $\frac{d\mathbf{x}(t)}{dt} = \gamma\mathbf{x}(t)\big(1-\mathbf{x}(t)\big)$.

c) Network-diffusion model: Trans-neuronal spread along connected sites was modeled [6] as a "network heat equation" $\frac{d\mathbf{x}(t)}{dt} = -\beta\mathrm{H}\mathbf{x}(t)$ where H is the graph Laplacian [6]. Its solution via matrix exponentiation is $\mathbf{x}(t) = e^{-\beta H t}\,\mathbf{x}_0$.

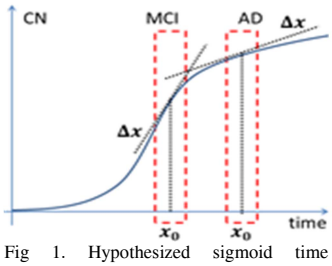

Fig 1. Hypothesized sigmoid time evolution of atrophy, demonstrating the time- and stage-dependent relationship between atrophy and its slope.

Prediction of future atrophy patterns For each subject:

- Baseline MRI volumetrics = x_0
- End-of-study volumetrics = $x^{obs}(t_{end})$
- Slope (atrophy rates) of each region independently were computed: Δx^{obs}
- Equations in a)-c) above were used applied to x_0 to obtain the predicted slope in each model: Δx^{pred}
- Δx^{obs} and Δx^{pred} were correlated over all regions (Pearson's R)

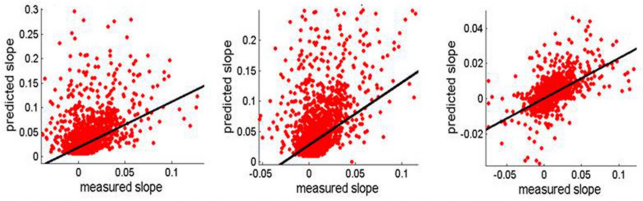

Fig 2: The slope of atrophy as predicted from baseline atrophy, using 3 alternate models: exponential (left), sigmoid (middle), and network-diffusion (right). R of correlation is: 0.19, 0.31, 0.65 (resp). Each dot represents 1 out of 86 regions of 1 out of 687 subjects.

Results: Pearson correlation of measured rate of change of atrophy in each region of each subject over the study duration, and its slope as predicted by the 3 models is shown in Fig 2. Only regions which show measurable atrophy (above zero z-scores) at baseline were used in the analysis in order to suppress noise from volumetric data. High correlation value would imply that the model captured the atrophy-slope relationship accurately. Pearson's R was 0.19 for the exponential model and 0.31 for the sigmoid model. This compares favorably with the network-diffusion model, which achieved R of 0.65. The difference in R between all 3 models was statistically highly significant, judging from Fisher's R-to-z transform and its p-values. For the purpose of this analysis, both MCI and AD subjects from ADNI database were used, since the objective is to deduce the atrophy-slope relationship irrespective of disease stage.

Discussion: Assuming that Pearson correlation between predicted and measured atrophy slope is a reasonable proxy for the quality of each model, we conclude that the network-diffusion model stands validated, and is significantly superior to non-network alternative models, *viz* exponential and sigmoid evolution. Given that the alternate models represent established and popular hypotheses in the field of neurodegeneration, these results assume added importance. They suggest that without considering the effect of networked transmission of pathology, it is not possible to fully characterize the progression of dementia. The rate of change of atrophy is well-known to have a complicated and spatially-dependent relationship to atrophy itself [8]. If vindicated by future experiments, these results would suggest that the relationship only appears complicated in absence of the network, and that once the network progression is accounted for, the relationship becomes straightforward. Success in capturing this topographic effect of atrophy 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 [7,8]. 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. To our knowledge this is the first fully quantitative head-to-head test of different models of degenerative progression in the brain.

References:

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