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Highlights

- Trans-neuronal "prion-like" progression of degeneration can be captured mathematically via a network-diffusion model
- Model recapitulates classical patterns of atrophy seen in dementias
- We will describe this technology and its use in predicting future <u>atrophy</u>

Title: *Predicting Neurodegenerative Disease with Connectomics*

Fig 1: Measured atrophy patterns in AD and bvFTD (top) appears to match well with the 2nd and 3rd eigen-modes of brain network (bottom).

Target audience: – We believe that researchers and clinicians involved in neuroimaging of neurodegenerative diseases can benefit from a deeper understanding of this exciting new technology.

OUTCOME/Objectives: Apply brain connectomics data for modeling and predicting the patterns of atrophy in neurodegeneration. Appreciate a new understanding of transneuronal spread, and how such mechanisms can be captured mathematically.

PURPOSE: Prion-like proteopathy[1] of dementias suggest transmission along fiber pathways of the brain network. In a recent paper [2] we modeled the macroscopic consequences of network-centric propagation as a diffusion process on the structural (tractography-derived) brain network. The model accurately recapitulated known patterns of atrophy seen in several dementias. To our knowledge network diffusion constitutes the first fully quantitative, testable model of macroscopic transmission of degenerative processes in the brain. Here we highlight this new advance, put it in the wider context of graph theoretic modeling of dementias and demonstrate how its use for the prediction of future disease patterns.

METHODS: Given the brain's connectivity matrix ("connectome") $C = \{c_{i,j}\}$, where i and j are node labels corresponding to different structures in the brain. We hypothesize that the regional brain atrophy of diseased subjects, given by the vector $\mathbf{x}(t)$ at time t, evolves according to the "network heat equation" $\frac{d\mathbf{x}(t)}{dt} = -\beta H \mathbf{x}(t)$, where H is the graph Laplacian matrix. Its solution is $\mathbf{x}(t) = e^{-\beta H t} \mathbf{x}_0$. Given the eigenvalue decomposition $H = U \Lambda U^\dagger$, where $U = [\mathbf{u}_1 \quad \cdots \quad \mathbf{u}_N]$, we get $\mathbf{x}(t) = U e^{-\Lambda \beta t} U^\dagger \mathbf{x}_0 = \sum_{i=1}^{n}(e^{-\beta \lambda_i t} \mathbf{u}_i^\dagger \mathbf{x}_0) \mathbf{u}_i$. The λ_i are eigenvalues of the Laplacian H. Clearly, only the eigen-modes $\mathbf{u}_i$ corresponding to very small eigenvalues will persist due to the exponentiation term.

RESULTS: These spatially distinct "persistent eigen-modes" were found to be homologous to atrophy patterns seen in common dementias: normal aging (19 subjects), Alzheimers (AD, 18 subjects) and fronto-temporal dementia (bvFTD, 18 subjects) - Fig 1 taken from [2]. Fig 2 shows close match between relative prevalence rates of various dementias and the strength of various eigen-modes. Predictive power of future atrophy patterns is part of ongoing work, and shows tremendous promise when applied to ADNI and other longitudinal dementia data.

DISCUSSION: These results could explain why degeneration appears to affect distinct and specific sub-networks in the brain [3], as a simple consequence of the brain's eigenmodes. The model makes specific predictions about the relative prevalence rates of various dementias, which are borne out by published data. Finally, the model can be used to predict future atrophic patterns of any patient using baseline neuroimaging data.

CONCLUSION: These results support the hypothesis that all classical dementias might be simply a result of *graph dynamics, with* various dementias being merely different "eigen-modes" of the diffusion process, with no need for specific focal location, nor region-specific predilection in dementia. Here we stress the clinical application of predicting future atrophy patterns from baseline MRI scans.

Fig 2: Left: published relative prevalence rate of various dementias vs. survival time $1/\lambda_i$. Right: Publishedprevalence of AD and bvFTD (dots) as a function of age, along with parameter-optimized model prediction (curves).

REFERENCES: [1] Frost and Diamond, *Nat Rev Neurosci* 11(3):155-9
[2] Raj A, Kuceyeski A, Weiner M, Neuron 2012; 73, 1204–15
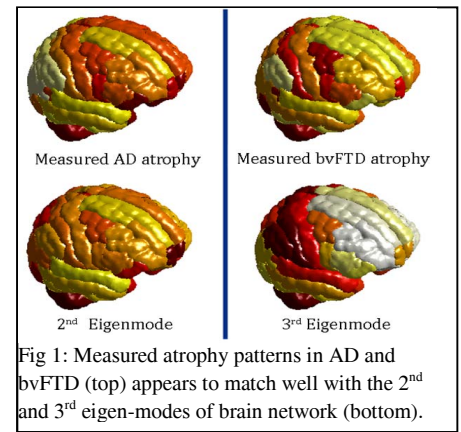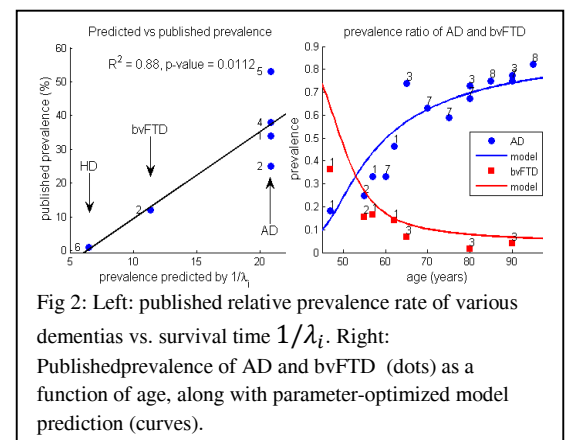[3] Zhou, et al. Neuron 2012; 73, 1216–27