Graph Diffusion

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Purpose: Recent studies on 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. Its neurologic impact arises from its implication that diverse proteopathic etiologies could produce shared spatial patterns whose explanation requires neither selective vulnerability [3] nor focal points of origin [4], nor differential stressor loads [5]. Here we highlight this new advance and put it in the wider context of graph theoretic modeling of dementias. We believe that researchers involved in neuroimaging of neurodegenerative diseases can benefit from a deeper understanding of this exciting new technology.

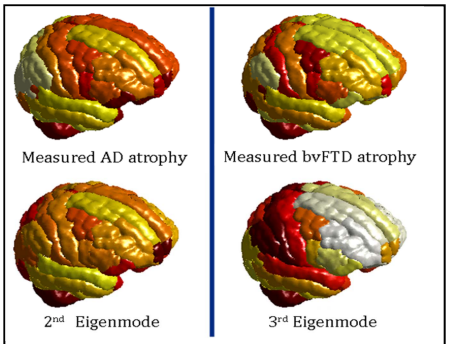

Fig 1: Measured atrophy patterns in AD and bvFTD (top) appears to match well with the 2nd and 3rd eigen-modes of brain network (bottom).

Outline of content:

A. *Overview of new bench research* implicating trans-neuronal transmission of misfolded proteins in neurodegenerative diseases [1,3,4,5] as a motivation for looking at network-level transmission models.

B. *Mathematical Description of a network-diffusion model of dementia propagation*. We will derive how diffusion on the brain's connectivity network can give a simple model of the dynamics of dementia, as follows. 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" $\frac{d\mathbf{x}(t)}{dt} = -\beta \mathrm{H}\mathbf{x}(t)$, where H is the graph Laplacian matrix : $H_{i,j} = \begin{cases} -c_{i,j} & for\ c_{i,j} \neq 0 \\ \sum_{i,j':e_{i,j'} \in \varepsilon} c_{i,j'} & for\ i = j \\ 0 & otherwise \end{cases}$. Its solution via matrix exponentiation 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; the smallest one is 0 and a few are close to 0. Clearly, the eigen-modes $\mathbf{u}_i$ corresponding to large eigenvalues will quickly disappear after a short period of time due to the exponentiation term, leaving only the small eigen-modes, which will persist.

C. *Summary of results and predictions*. 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 the corresponding correlation plots, with p-values which clearly support our hypothesis. Fig 3 shows close match between relative prevalence rates of various dementias and those predicted by the strength $1/\lambda_i$ of various eigen-modes.

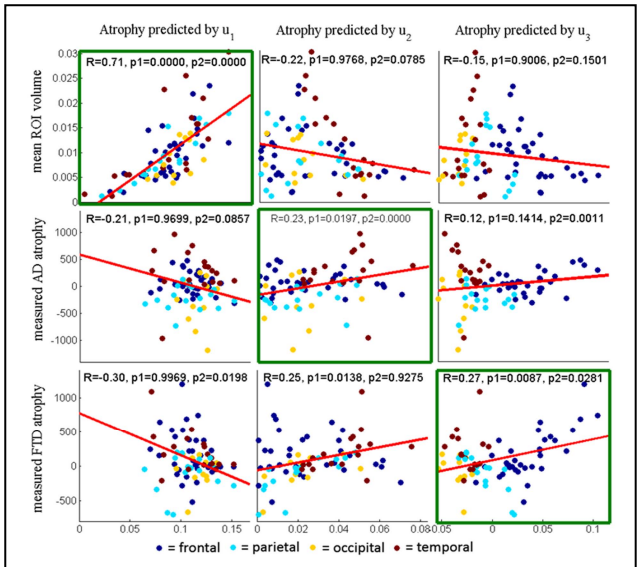

Fig 2: Correlation between measured atrophy and network diffusion eigen-modes. Significant correlations are depicted by green boxes. The association is along the diagonal, implying that there is a one-to-one correspondence between eigen-modes and dementias.

D. *Discussion of implications*. 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.

E. *Comparison with other related investigations*. We highlight some closely related publications [4,6] which used fMRI-derived functional networks to explore the relationship between brain networks and dementia. They conclude that the trans-neuronal transmission model best describes their data, in consonance with our findings. We set this and other papers in the context of neurodegeneration.

F. Finally, we will explore *other brain disorders* that can benefit from this kind of network dynamic modeling. In particular we will explore epilepsy and Parkinson's, both of which are considered diseases involving the spread of toxicity in the brain.

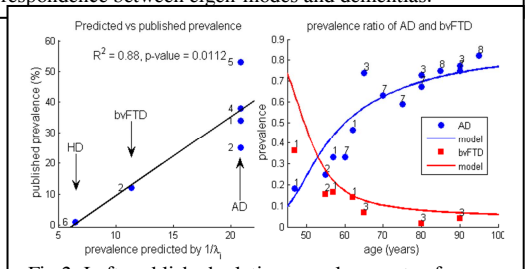

Fig 3: Left: published relative prevalence rate of various dementias vs. survival time $1/\lambda_i$. Right: Publishedprevalence of AD and bvFTD (dots) as a function of age, along with parameter-optimized model prediction (curves).

Summary: Observed homologies between eigen-modes and dementia atrophy 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. This leads to the provocative but plausible idea that neurodegeneration may not have to have a specific focal location, nor region-specific predilection. In this presentation we will stress the clinical utility of these network models: that that can predict future atrophy patterns of individual patients from baseline MRI scans.

[1] Frost and Diamond, *Nat Rev Neurosci* 11(3):155-9 [2] Raj et al, Neuron 2012; 73, 1204–15
[3] Seeley et al, Neuron 2009; 62:42-52 [4] Braak et al, Annals NYAS 2000; 924:53-61
[5] Saxena et al, Neuron 2011; 71(1):35-48 [6] Zhou et al. Neuron 2012; 73, 1216–27