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Modeling Progression in Neurodegenerative Diseases Using Network Connectivity

Or, How to use graph theory to describe neurodegenerative spread

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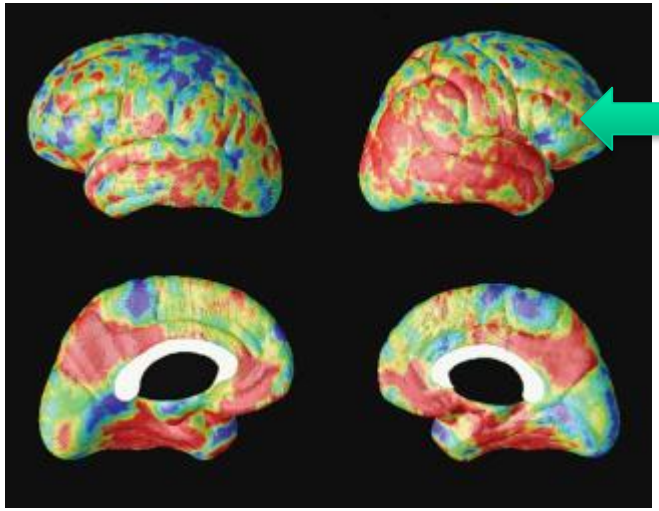
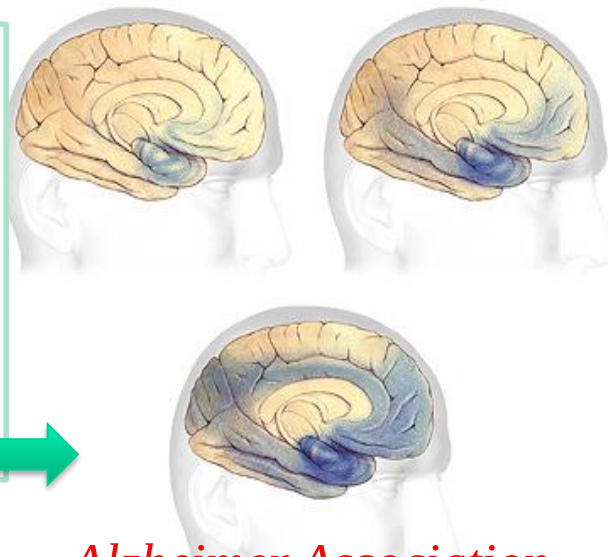
Neurodegeneration is a network disease



Apostolova, Arch Neurol 2007

- *Stereotyped atrophy patterns, not random*
- *(but considerable variations amongst patients)*
- *Braak staging model of AD, PD*
- *Caused by stereotyped spread of misfolded proteins (A-beta, tau, alpha-syn)*



Alzheimer Association

- *Insight: pathology travels along the brain's anatomic network connections*
  - *Eisele 2013, Clavaguera 2009, Harris 2010, Ahmed 2015 …*

- We can mathematically capture the emerging science of trans-neuronal transmission of misfolded proteins

Anatomic connectivity predicts Alzheimer patterns

REVIEW ARTICLE

Front. Aging Neurosci., 21 May 2015 | http://dx.doi.org/10.3389/fnagi.2015.00090

On the central role of brain connectivity in neurodegenerative disease progression

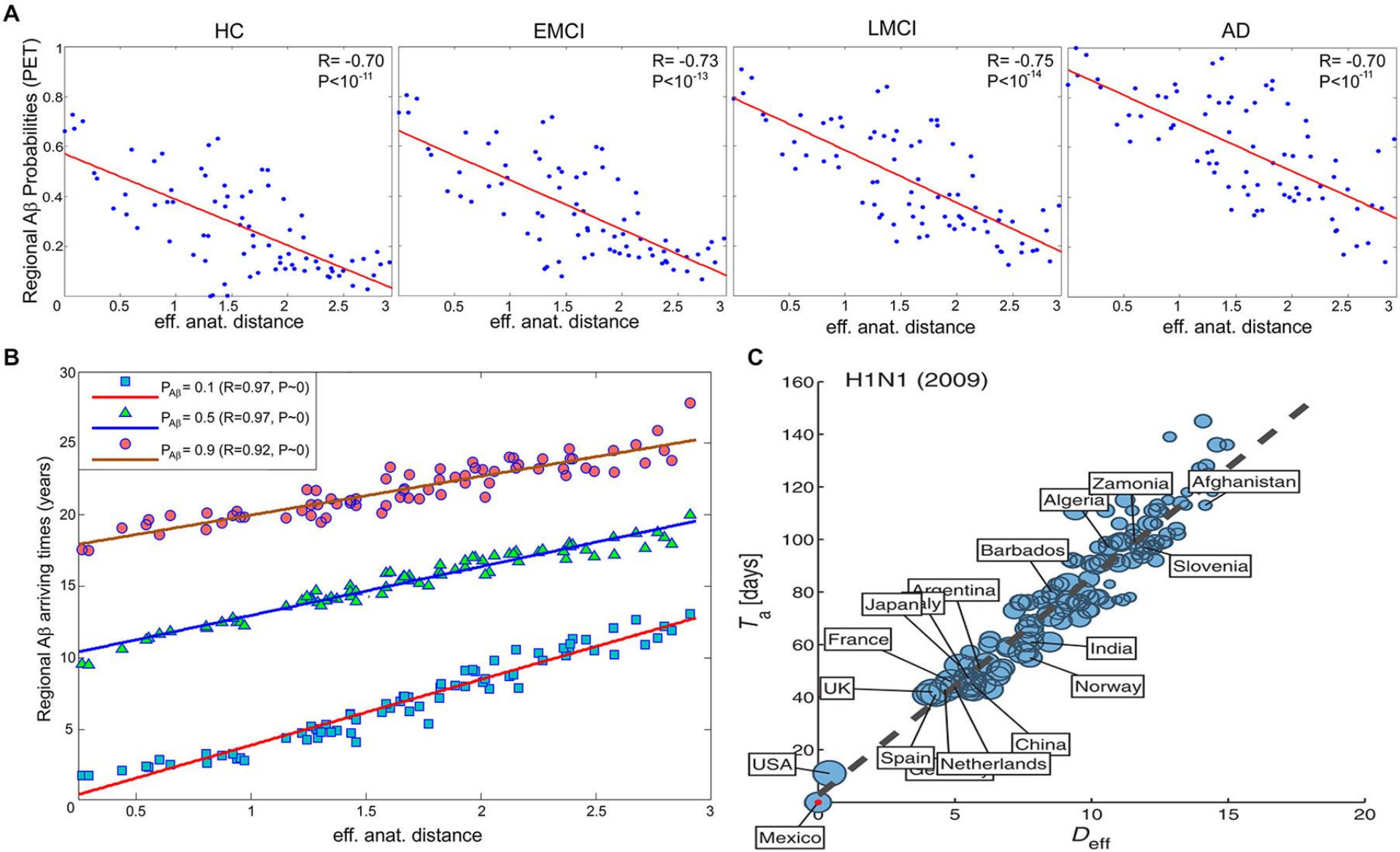
Yasser Iturria-Medina[1,2*] **and** **Alan C. Evans**[1,2]

[1]Montreal Neurological Institute, Montreal, QC, Canada

[2]Ludmer Center for NeuroInformatics and Mental Health, Montreal, QC, Canada

- Nice neuroimaging-relevant review
- There is a strong effect of connectivity on Alzheimer's disease (AD) regional distribution.

Fig 3 from Iturria-Medina and Evans:

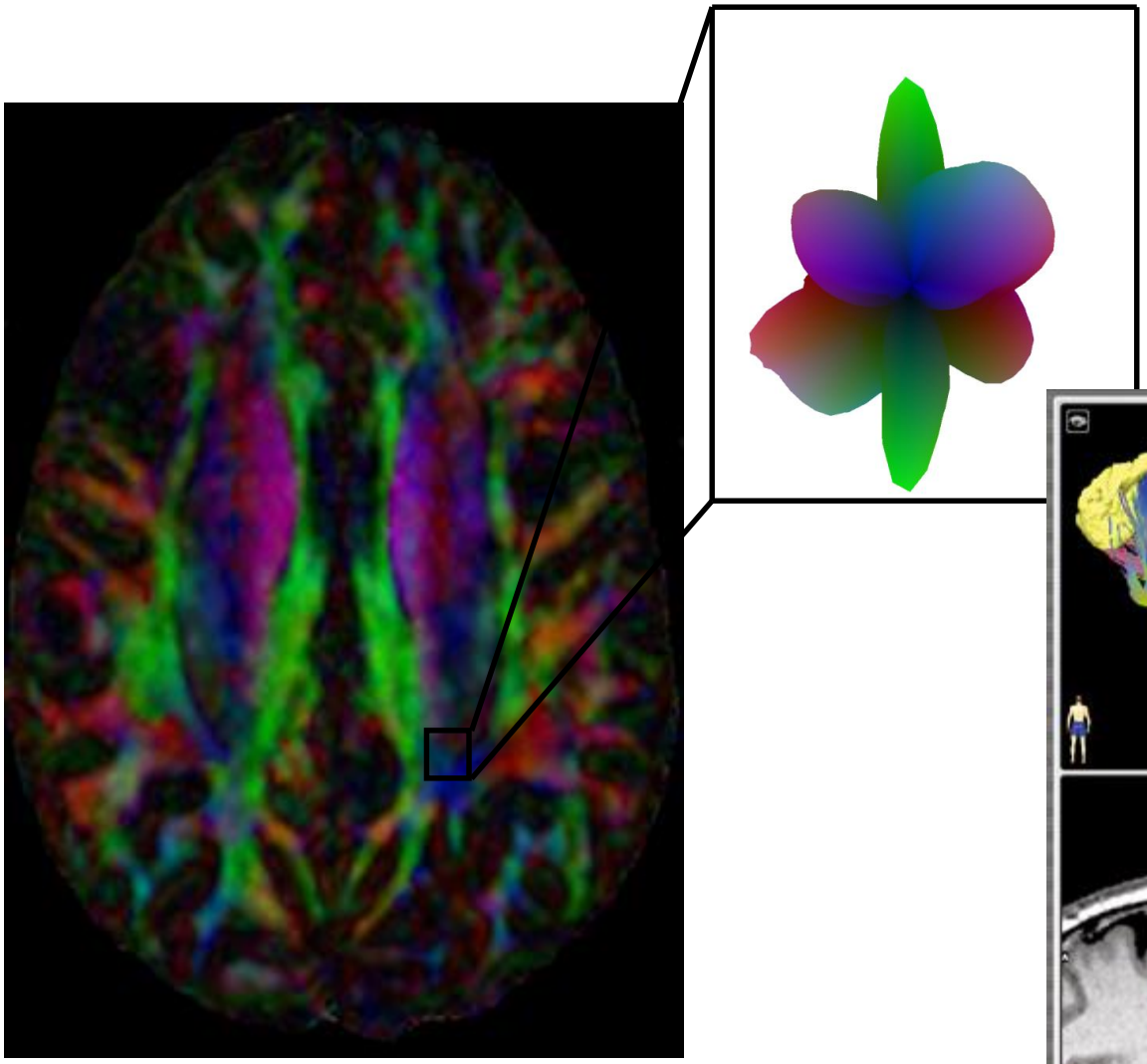


"Prion-like" trans-neuronal transmission of degenerative pathologies

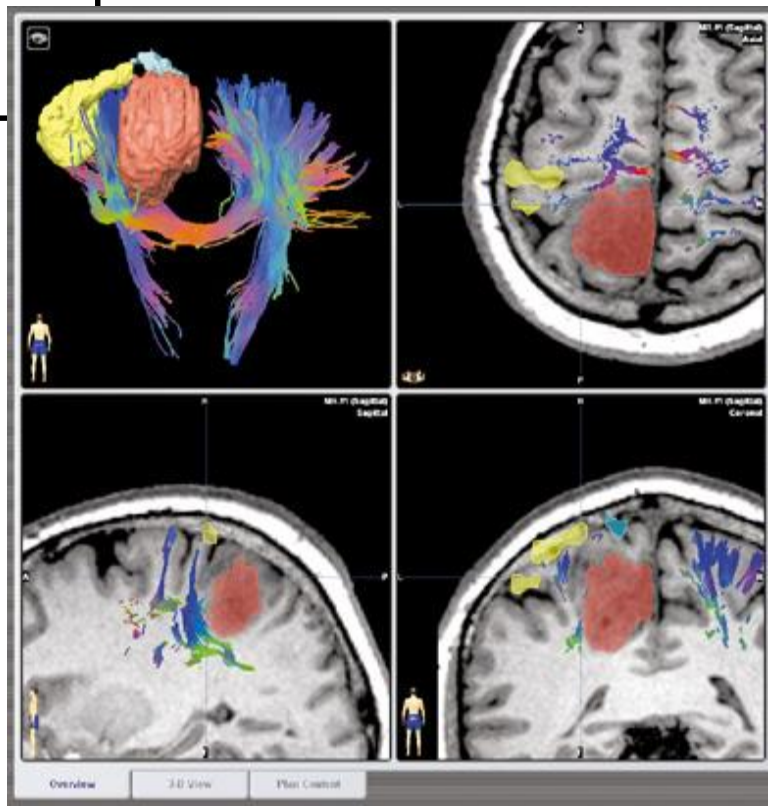
- Patterns of atrophy, tau and amyloid in Alzheimer brain are stereotyped
  - Braak, H., and Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. *82*, 239–259.
- Misfolded proteins appear to propagate trans-neuronally, along fiber tracts
  - Frost, B., and Diamond, M.I. (2010). Prion-like mechanisms in neurodegenerative diseases. Nat. Rev. Neurosci. *11*, 155–159.
  - Iba, M., et al (2015). Tau pathology spread in PS19 tau transgenic mice following locus coeruleus (LC) injections of synthetic tau fibrils is determined by the LC's afferent and efferent connections. Acta Neuropathol. *130*.
  - Clavaguera, F., Bolmont, T., et al. (2009). Transmission and spreading of tauopathy in transgenic mouse brain. Nat. Cell Biol. *11*, 909–913.

Burgeoning bench science on network transmission

How to get the "connectome"?
High Angular Resolution Diffusion Imaging (dMRI)



credit: P Mukherjee



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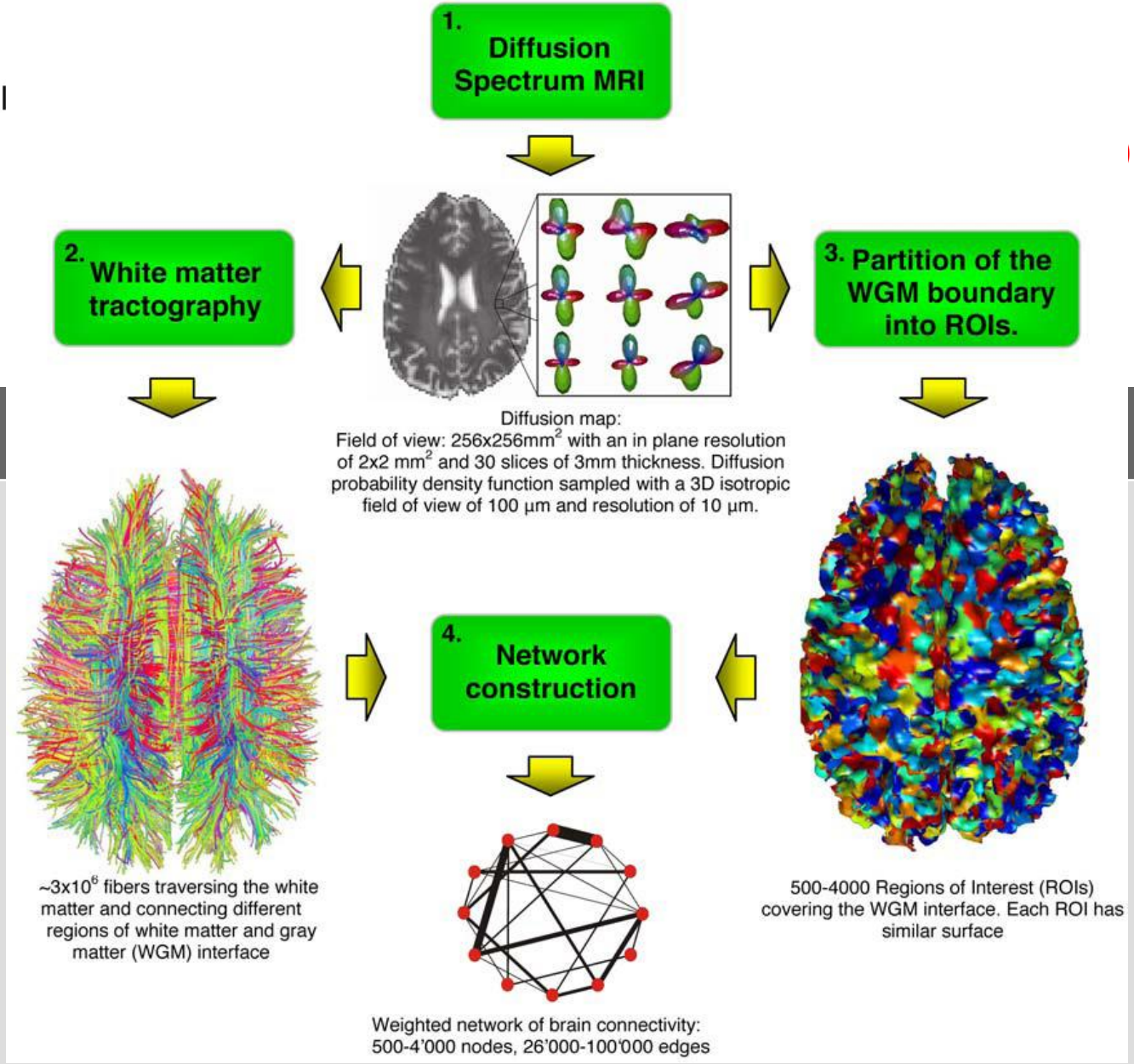
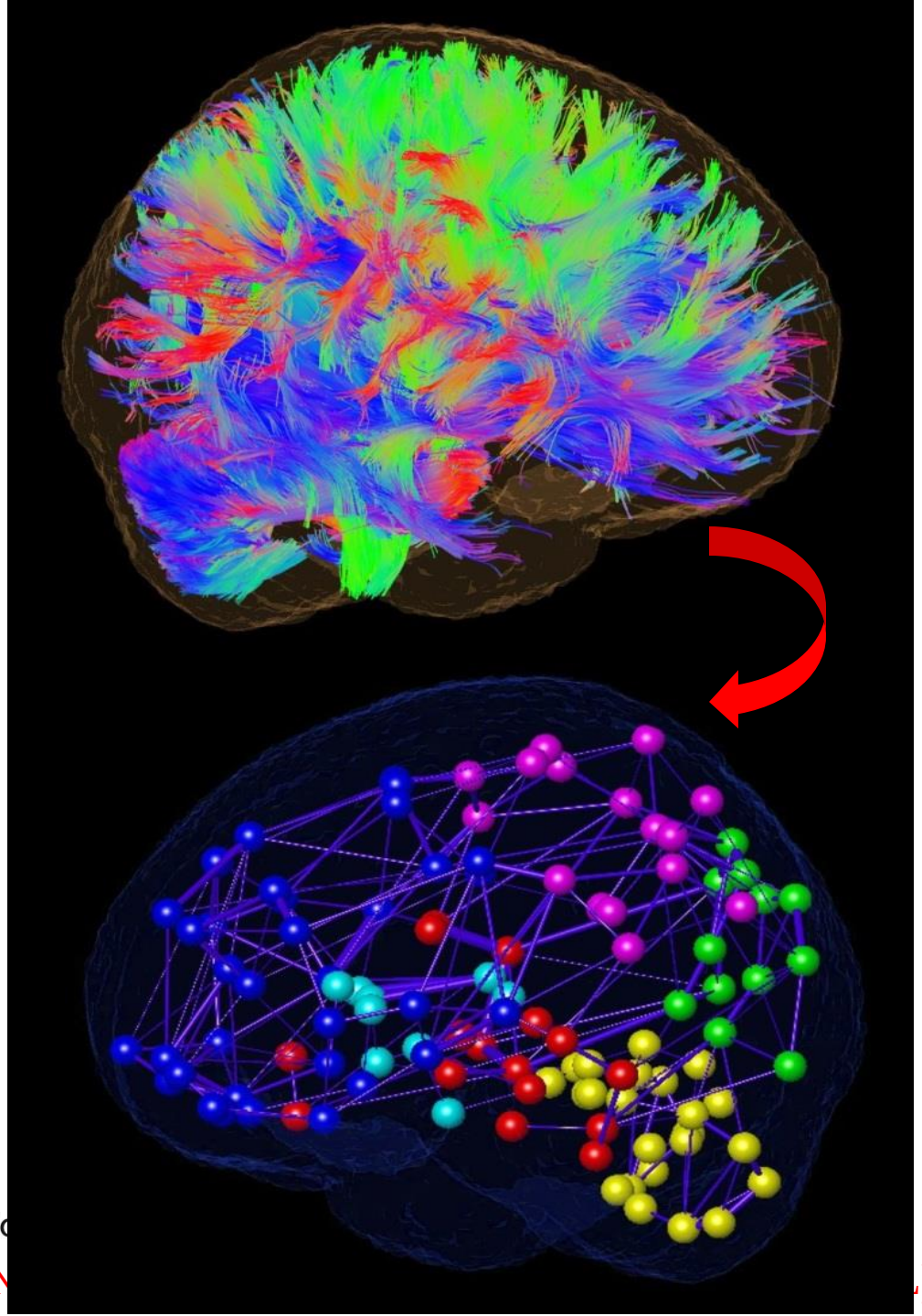


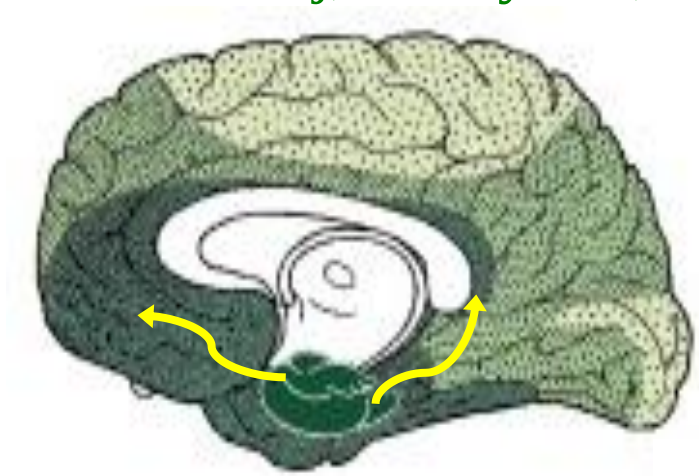
Mapping Human Whole-Brain Structural Networks with Diffusion MRI
Patric Hagmann, Maciej Kurant, Xavier Gigandet, Patrick Thiran, Van J. Wedeen, Reto Meuli, Jean-Philippe Thiran, PLoS ONE 2(7)

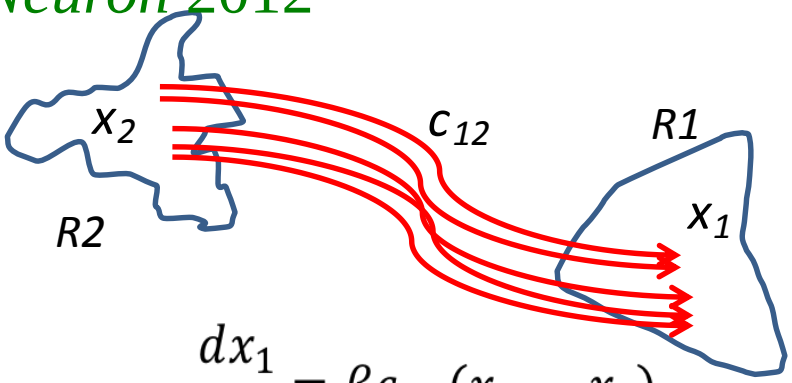
From DTI
to tractography
to network or “graph”



Diffusion on Graphs and Relationship to Dementias

- "Signal" x(t): amount of disease agent (Ab, tau, a-syn) in brain regions
- We mathematically model neurodegeneration as a diffusive process Raj, Kuceyeski, Weiner. *Neuron* 2012





$$\frac{dx_1}{dt} = \beta c_{1,2}(x_2 - x_1)$$

$$\frac{d\mathbf{x}(t)}{dt} = -\beta \mathrm{H}\mathbf{x}(t)$$

- ***Spread of tau pathology*** *from entorhinal cortex traces classic Braak stages.*
- *We model the trans-neuronal spread from region 2 to 1 as a diffusion process whose rate is regulated by network connectivity.*

- *Closed form solution:*

$$\mathbf{x}(t) = e^{-\beta H t}\,\mathbf{x}_0$$

Future spread pattern

Initial tau pattern

Graph "Eigenmodes" govern the patterns of neurodegeneration

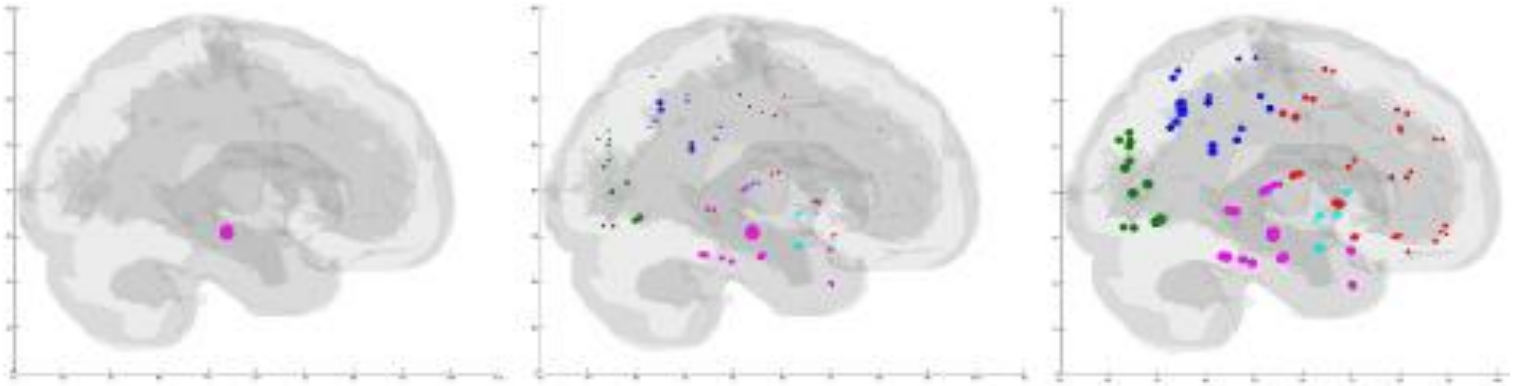
- From eigen-decomposition of H

$$\mathbf{x}(t) = U\, e^{-\Lambda\beta t} U^{\dagger}\mathbf{x}_0 = \sum_{i=1}^{N} (e^{-\beta\lambda_i t}\, \mathbf{u}_i^{\dagger}\mathbf{x}_0)\ \mathbf{u}_i$$

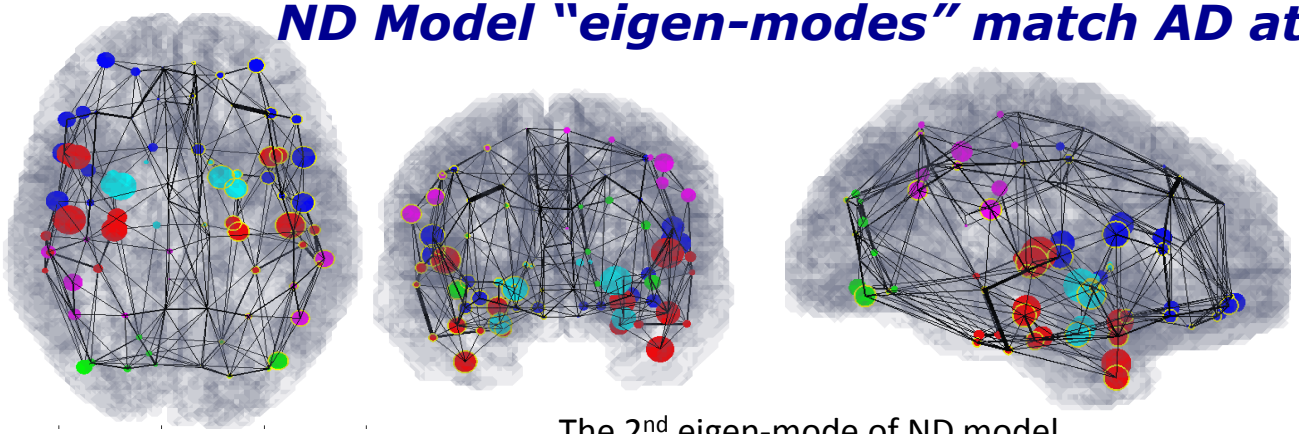
- Meaning that the solution of heat eqn is simply the sum of all eigen-modes u_i of H
- Larger eigenmodes decay away quickly
  - transient modes
- Only a few smallest eigenmodes persist
  - These modes might be primarily responsible for neurodegeneration

Raj, Kuceyeski, Weiner. Neuron 2012

ND Model seeded at Hippocampus recapitulates classic AD progression:

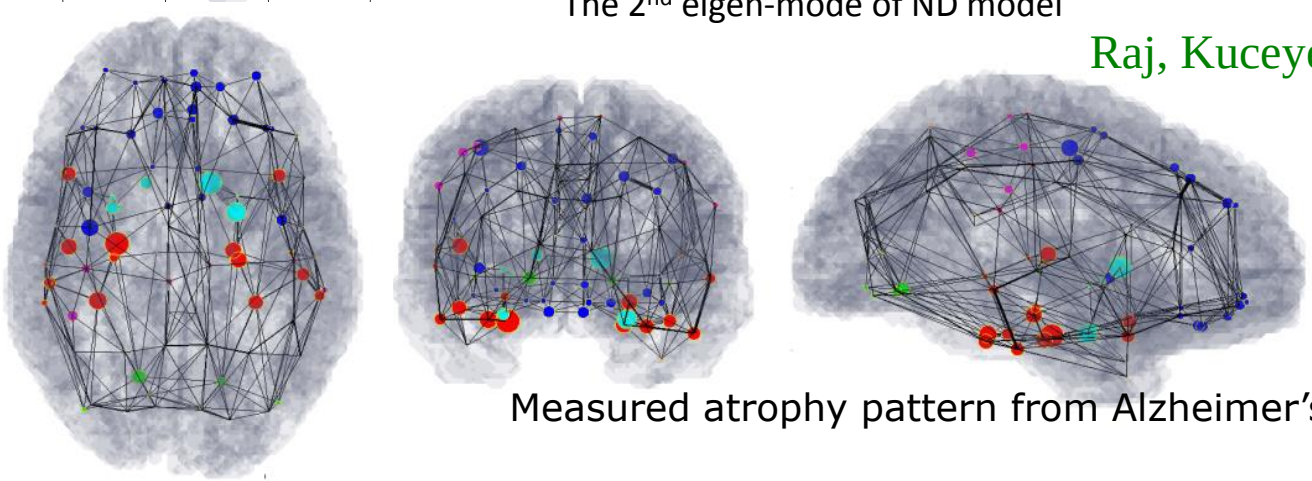


ND Model "eigen-modes" match AD atrophy topography:



The 2nd eigen-mode of ND model

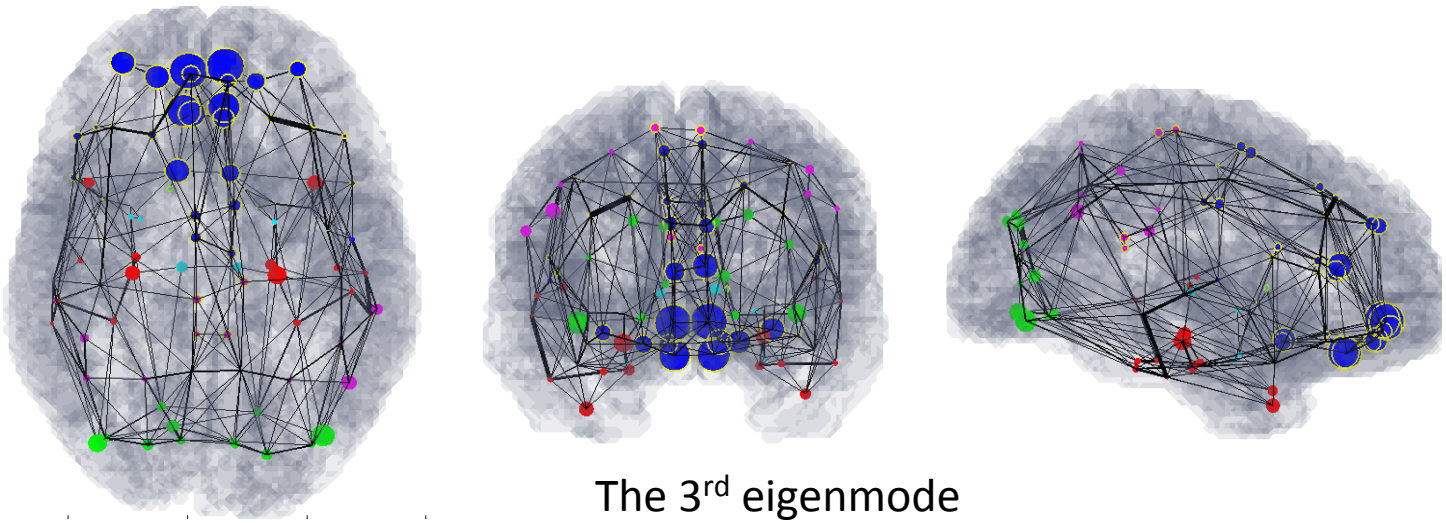
Raj, Kuceyeski, Weiner. Neuron 2012



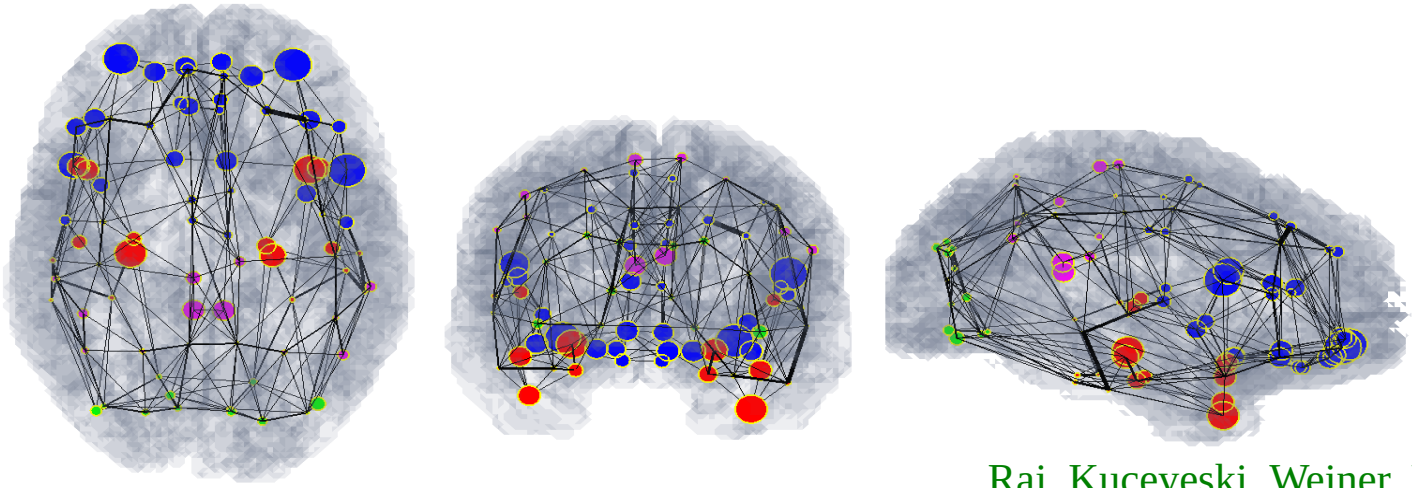
Measured atrophy pattern from Alzheimer's subjects

(IDEAL)

Eigenmode 3



The 3rd eigenmode

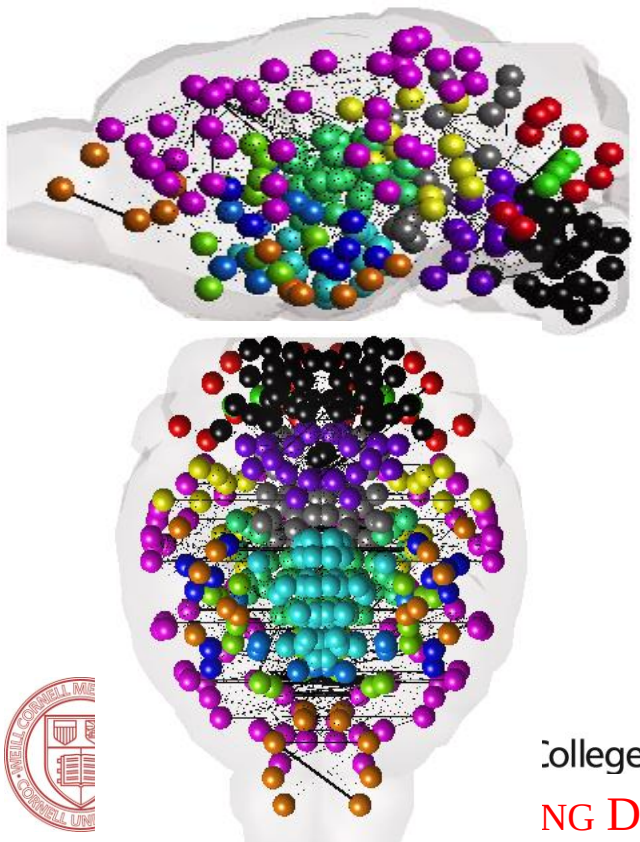


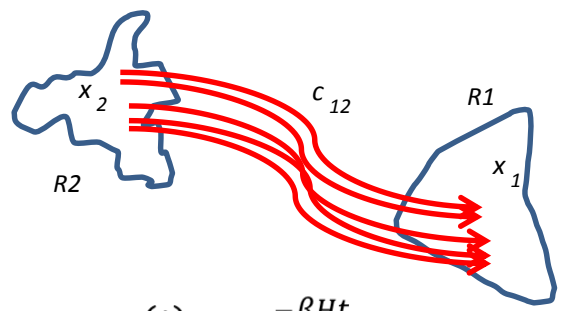
Raj, Kuceyeski, Weiner. Neuron 2012

bvFTD atrophy pattern measured by volumetric analysis

Network Diffusion Model applied to mouse histopathology

- *Mouse connectome from Allen Brain Institute study (Oh et al, Science 2014)*
- *Directional connectivity inferred from anterograde viral tracer*
  - *Engineered to express GFP natively, high affinity to synapsin.*
  - *The specific vector, rAAV1, travels exclusively along axons, across synapses, and through dendrites in the CNS*
  - *N = 1231 C57/BL6 males*
- *213-region parcellated mouse brain atlas ➔ 213x 213 (directional) connectivity*



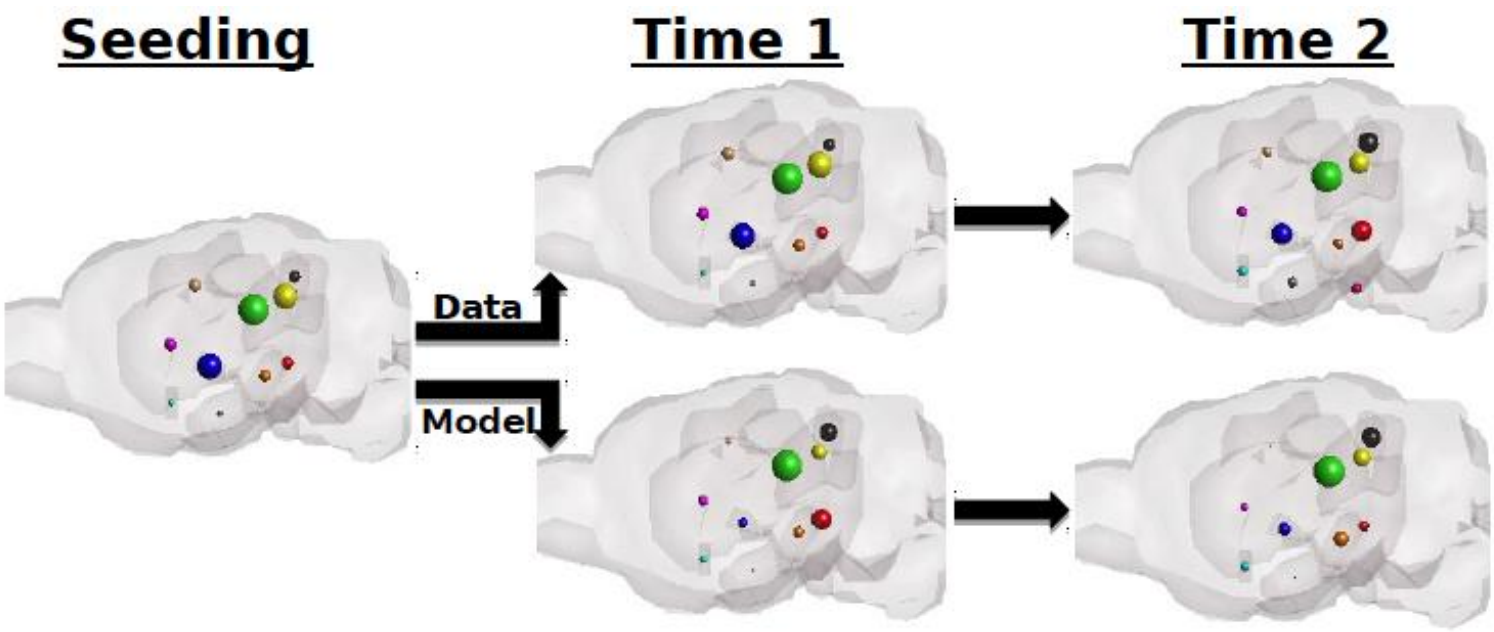


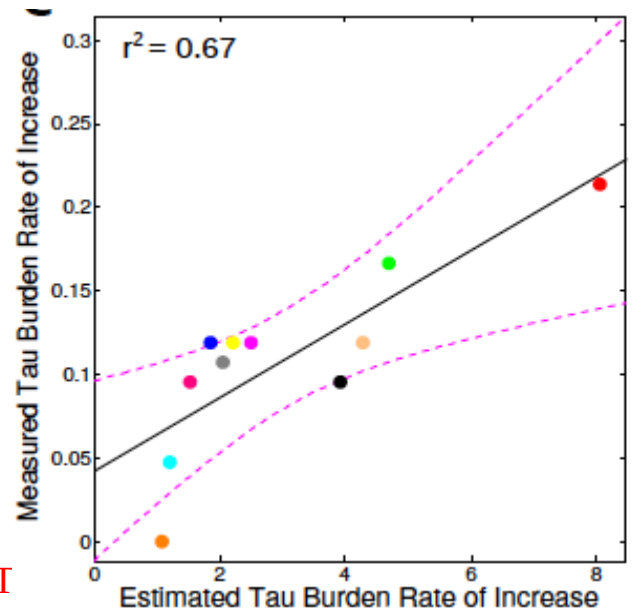
$$\mathbf{x}(t) = e^{-\beta H t}\,\mathbf{x}_0$$

Network-Diffusion model prediction

Steady state pathology distribution (eigenvectors)
Dynamics of pathology spread from inoculation region

Network Diffusion Model applied to mouse histopathology





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Network Diffusion model accurately predicts regional A-beta and tau distribution in transgenic mouse histopathology

Mezias et al, under review

Genetic effects: Comparing gene expression similarity v connectivity

- *Similarity of gene expression of a region to seed expression does not explain tau spread*

- *Best future tau predictor at baseline = connectivity to seed*

Running Network Diffusion model on connectivity and genetic similarity networks

Example: Hurtado

- *Connectivity "wins"*
- *Gene expression-driven model gives non-specific result*

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Predicting Future Atrophy Patterns

- 687-subject ADNI T1 volumetrics using Freesurfer and VBM
- 2-4 year longitudinal follow up scans available

Cell Reports
Article

OPEN ACCESS
CellPress

Network Diffusion Model of Progression Predicts Longitudinal Patterns of Atrophy and Metabolism in Alzheimer's Disease

Ashish Raj,[1,*] Eve LoCastro,[1] Amy Kuceyeski,[1] Duygu Tosun,[2] Norman Relkin,[3] and Michael Weiner,[2]
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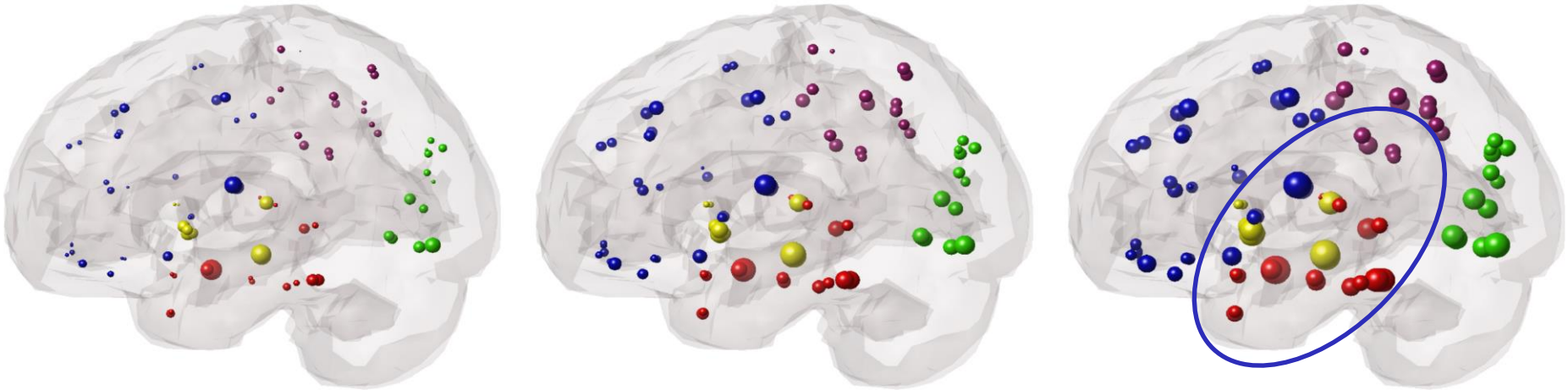
[1]Department of Radiology, Weill Medical College of Cornell University, 515 East 71 Street, Suite S123, New York, NY 10021, USA
[2]Department of Radiology and Biomedical Imaging, Center for Imaging of Neurodegenerative Diseases, University of California, San Francisco, 4150 Clement Street (114M), San Francisco, CA 94121, USA
[3]Department of Neurology and Neuroscience, Memory Disorders Program, Weill Medical College of Cornell University, 428 East 72nd Street, Suite 500, New York, NY 10021, USA
*Correspondence: ashish@med.cornell.edu
http://dx.doi.org/10.1016/j.celrep.2014.12.034

Predicting future disease patterns

- *Alzheimer's Disease Patient*

Predicted atrophy of AD, subject #5, t = 0, 5, 10, years



- *Baseline*

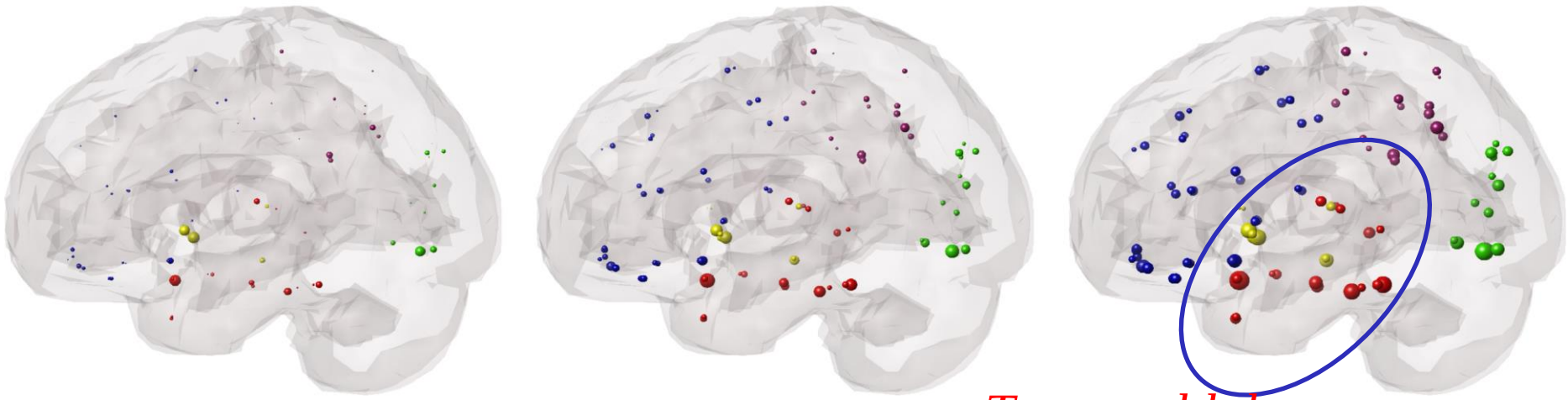
Projected: 5 years

10 years

Predicting future disease patterns

- *MCI subject who converted to AD*

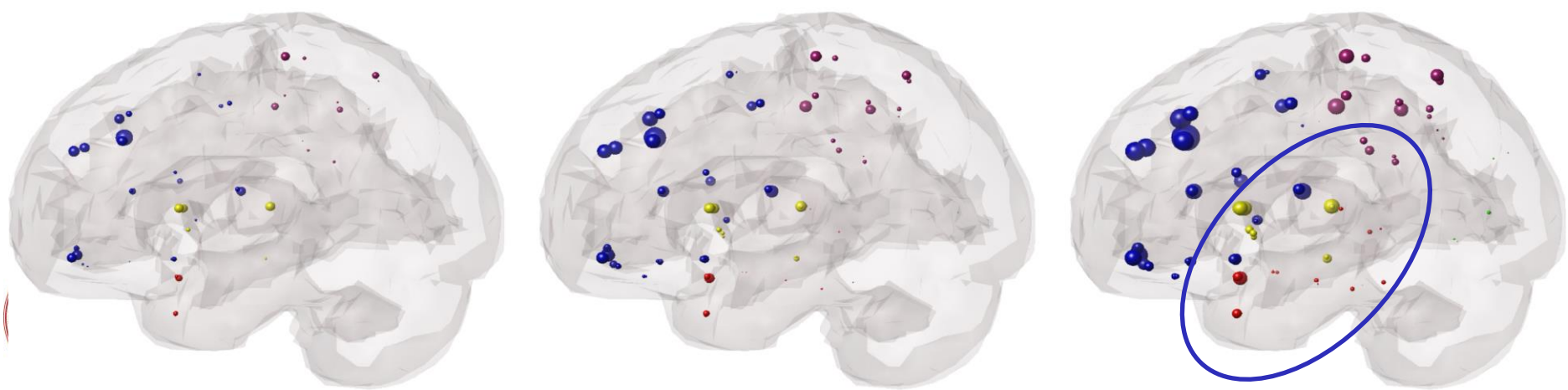
Predicted atrophy of MCI-C, subject #104, t = 0, 5, 10, years



- *Temporal lobe*

- *MCI subject who did not convert to AD*

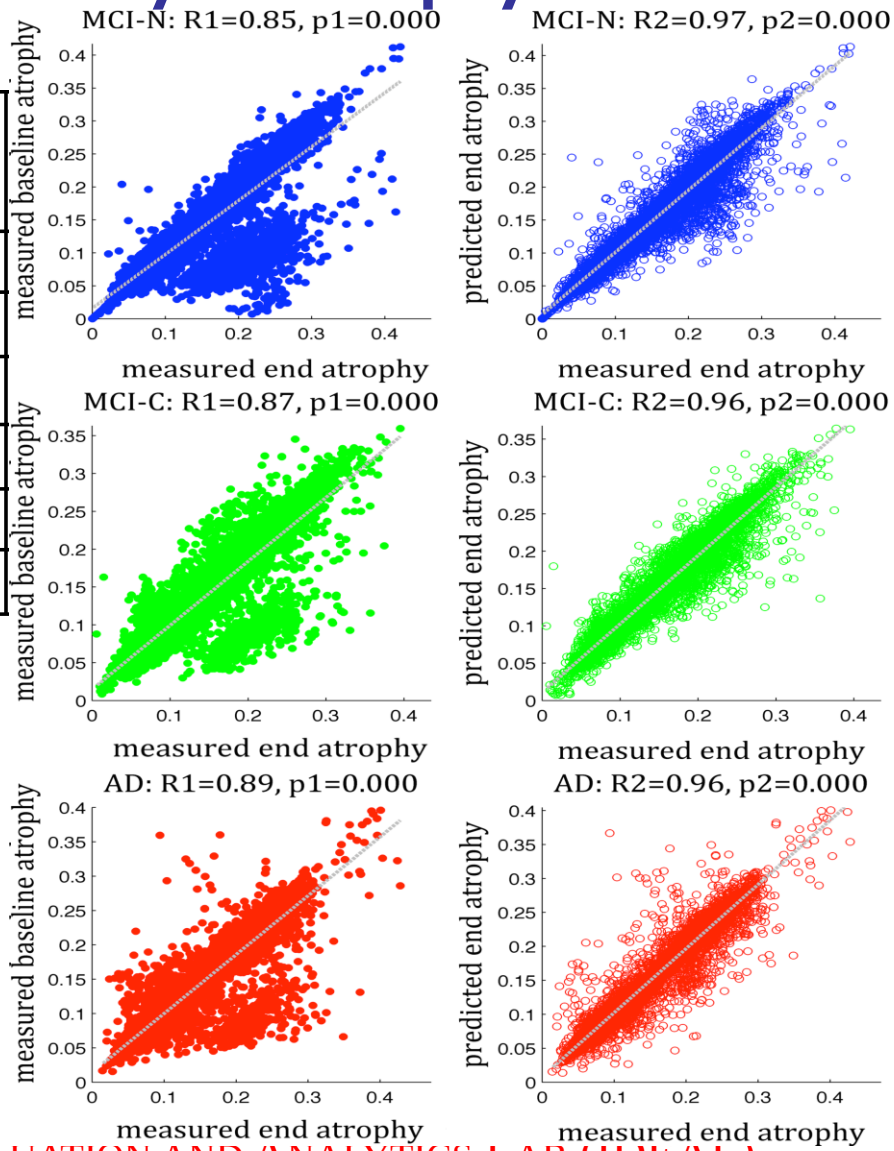
Predicted atrophy of MCI-N, subject #100, t = 0, 5, 10, years



Predicting future atrophy patterns

Significant improvement in correlation between measured and predicted out-year atrophy

Dataset	Stats (measured)	Stats (model)
MCI-N atrophy	0.85	0.97
MCI-C atrophy	0.87	0.96
AD atrophy	0.89	0.96
MCI-N FDG	0.92	0.96
MCI-C FDG	0.89	0.93
AD FDG	0.88	0.95



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Application in Clinical Trials

- A predictive computational biomarker has strong applicability in clinical trials, in two ways:

1. Cohort selection/enrichment: By extrapolating baseline scans of prospective cohort using our technology, subjects that are not on dementia track can be excluded
   - Saves lots of clinical trials $$

2. Trajectory monitoring: small drug-induced changes in current imaging endpoints are difficult to measure sensitively
   - need large N ➔ lots of $$
   - ND model can provide "expected trajectory" information, and changes can be measured against that
   - Need far fewer N ➔ save lost of $$

Can mathematical network models help us understand pathogenesis, inception, spread and the entire dynamical course of disease?

Many important questions in AD research remain unresolved:

- Why is progression of each species so stereotyped?
- Why do tau and Aβ pathology selectively target separate and specific structures in early stages,
- and why do they not co-localize until later stages?

- So far we used baseline patterns to predict future patterns

Start with completely healthy brain

Impose simple models of pathology production

- *A-beta is produced in proportion to neuronal activity*
- *Tau is produced diffusely throughout the brain*

Network transmission model of subsequent spread

Network model correctly predicts both early amyloid and atrophy distribution

- Group average (t-statistic) of ADNI-2 EMCI patients
  - Thanks to M. Weiner and D. Tosun, UCSF

Network model also correctly predicts early tau distribution

- T807-PET scans of 30 early subjects (SMC, MCI, AD)

Dynamics of the joint tau/amyloid model, starting from a healthy brain

Raj et al, submitted

Conclusions

- *Presented a mathematical approach to study degenerative processes*
- *Using graph theory, we can turn neurological and pathophysiological knowledge into testable math models*

Future Steps:

- *Network diffusion is simplest but not the only model of spread of disease*
  - *Epidemiological models, higher-order linear ODEs*
- Apply to other neurodegenerative diseases
  - HD, ALS, CBD, SD, LBD

Thanks

- Cornell
  - Amy Kuceyeski, PhD
  - Chris Mezias
  - Fontasha Powell
  - Eve LoCastro
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  - Farras Abdelnour, PhD
  - Michael Dayan, PhD
  - Claire Henchcliffe, MD
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  - Michael Weiner, MD
  - Duygu Tosun, PhD
  - Pratik Mukherjee, MD-PhD
  - Norbert Schuff, PhD
  - Yu Zhang, MD

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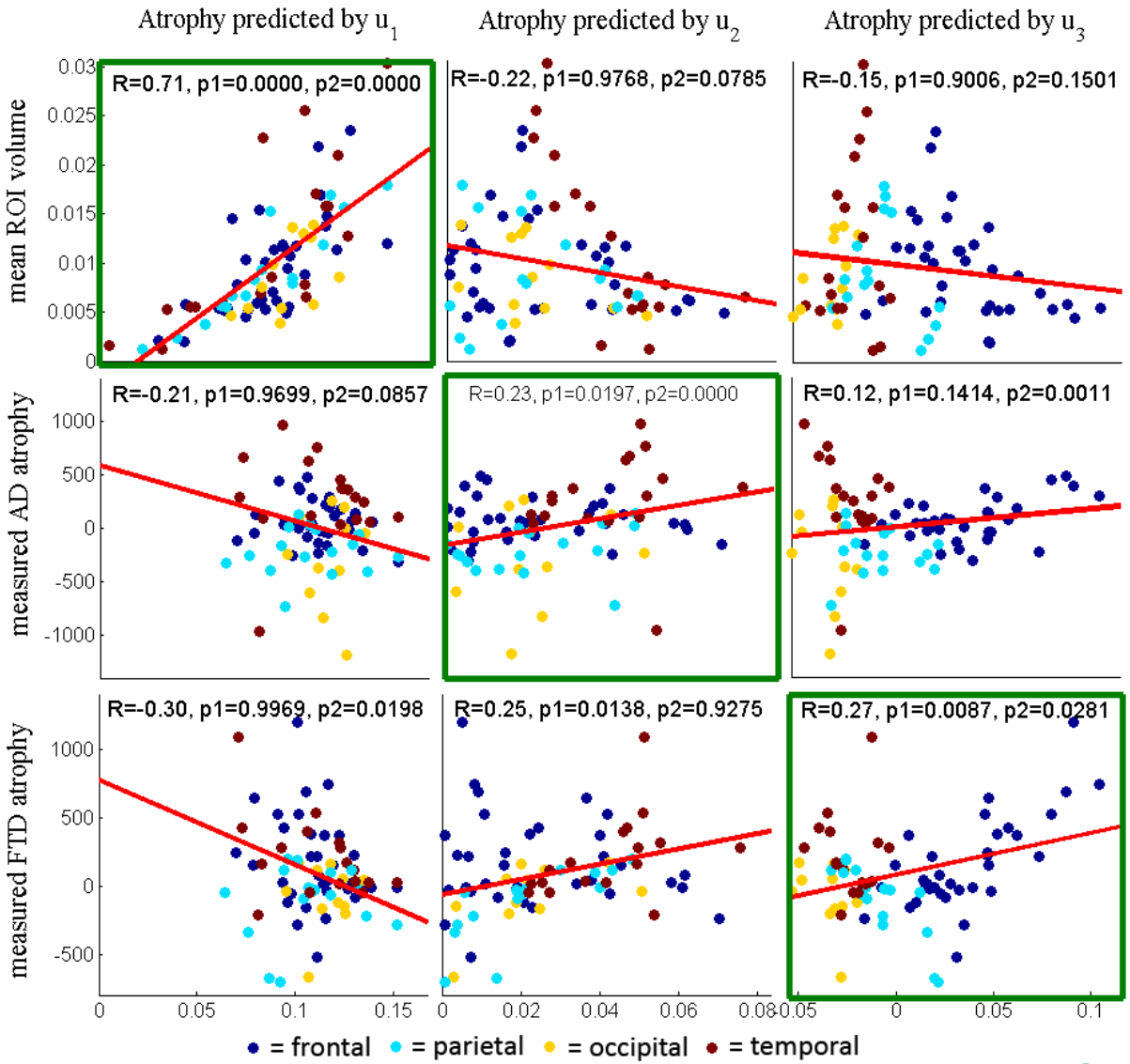
- *NIBIB Research Resource #P41 RR023953, Weiner (PI)*

For public data sharing, thanks to

- *Alzheimer's Disease Neuroimaging Initiative (ADNI)*
- *Parkinson's Progressive Marker Initiative (PPMI)*
- *Allen Brain Institute*

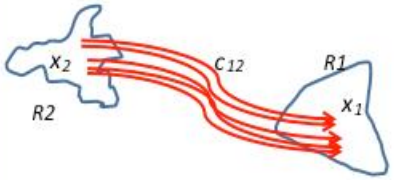
Statistical correlation analysis



Raj, Kuceyeski, Weiner. Neuron 2012

Parkinson's Disease

Synuclein spread in PD brain



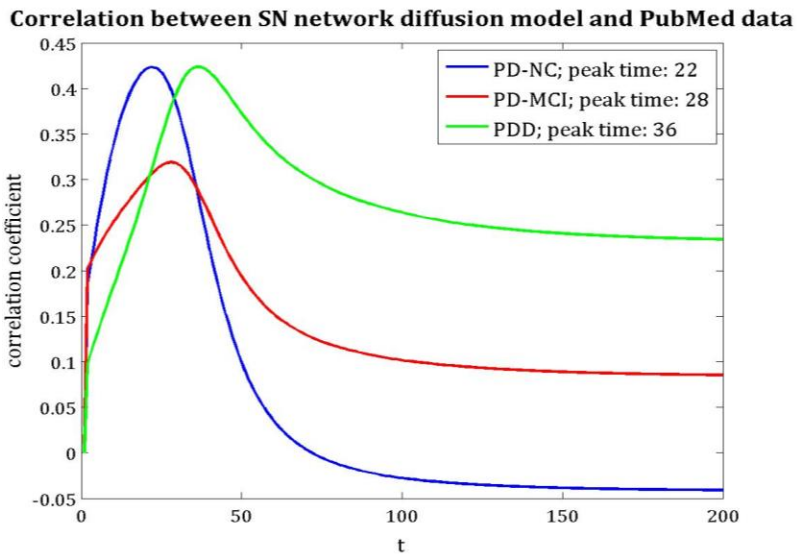
$$\frac{dx_1}{dt} = \beta c_{1,2}(x_2 - x_1)$$

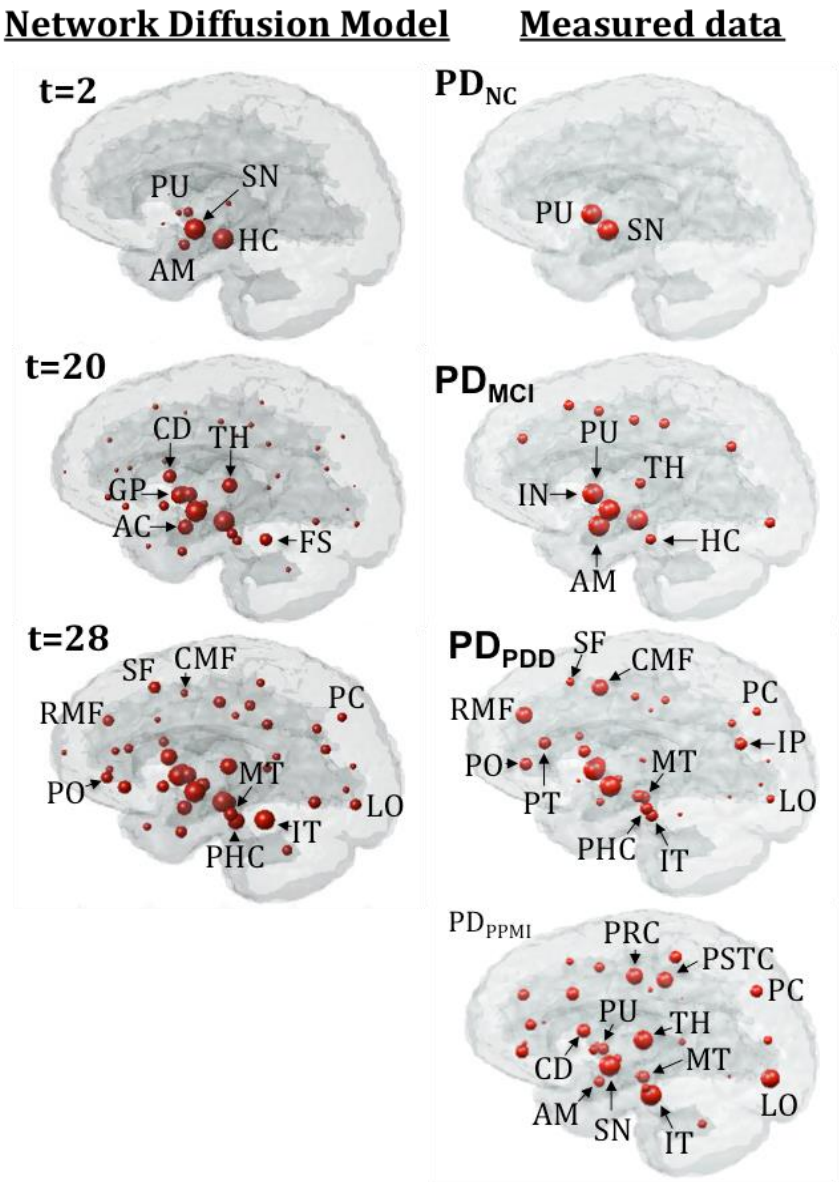
Diffusion model governing synuclein spread

Spread of Parkinson's pathology traces 6 Braak stages (left). This spread from region 2 to 1 is modeled as a diffusion process whose rate is regulated by network connectivity.

- *Parkinson's disease is initiated at substantia nigra, then spreads outwards*
- *Network diffusion seeded at SN ➔ predict future PD pathology*

Network diffusion captures stereotyped PD topography





Correlation between Pubmed and model at various diffusion times. PU=putamen, TH=thalamus, AM=amygdala, HC=hippocampus, CD=caudate, IN=insula, ENT=entorhinal