Disease Knowledge Transfer across Neurodegenerative Diseases

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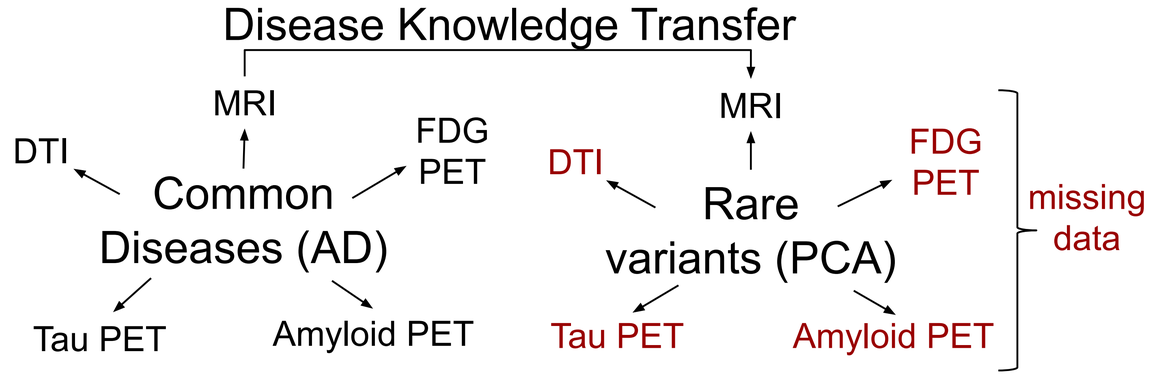
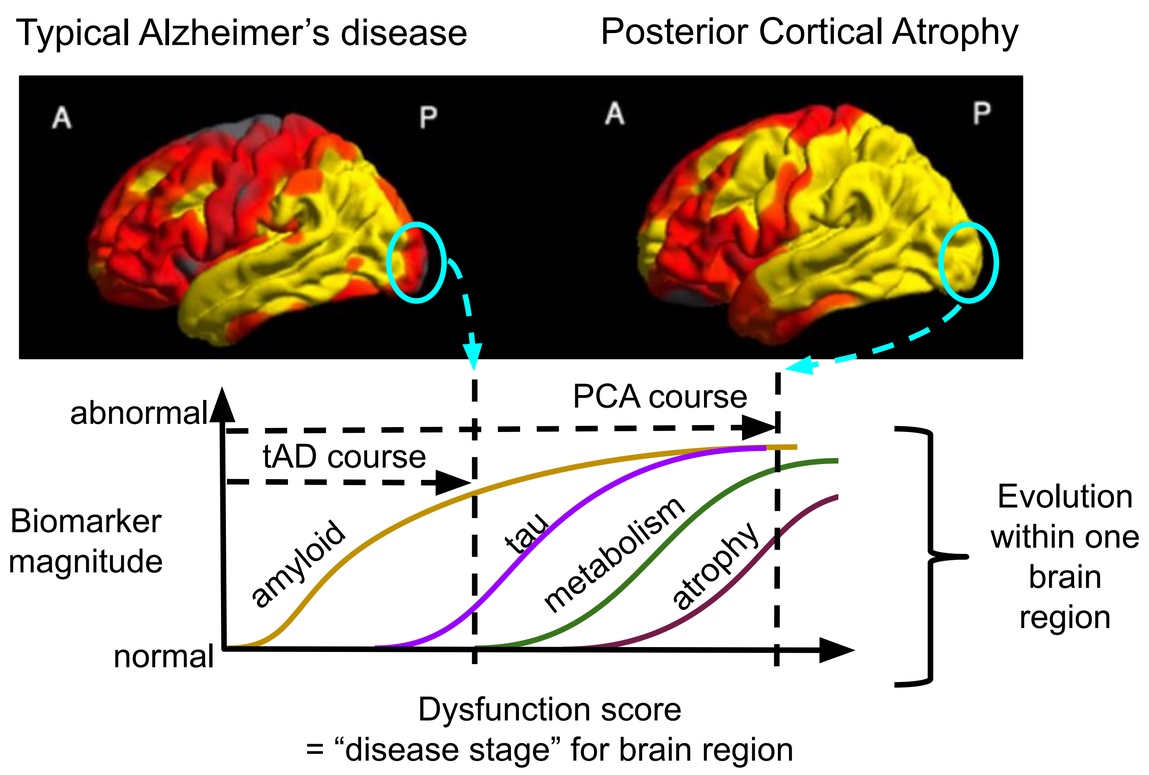
Aim Infer progression of multimodal biomarkers in rare neurodegenerative diseases (NDs) by leveraging larger datasets of common, related variants.

Why Posterior Cortical Atrophy (PCA): progression of multimodal biomarkers not known → Identify outcome measures and suitable subjects for PCA clinical trials



1. Intuition

- Diseases affect different brain regions un-equally, but underlying mechanisms are the same (amyloid cascade)
- **Idea:** each brain region follows "its own disease course", common across diseases → dysfunction score



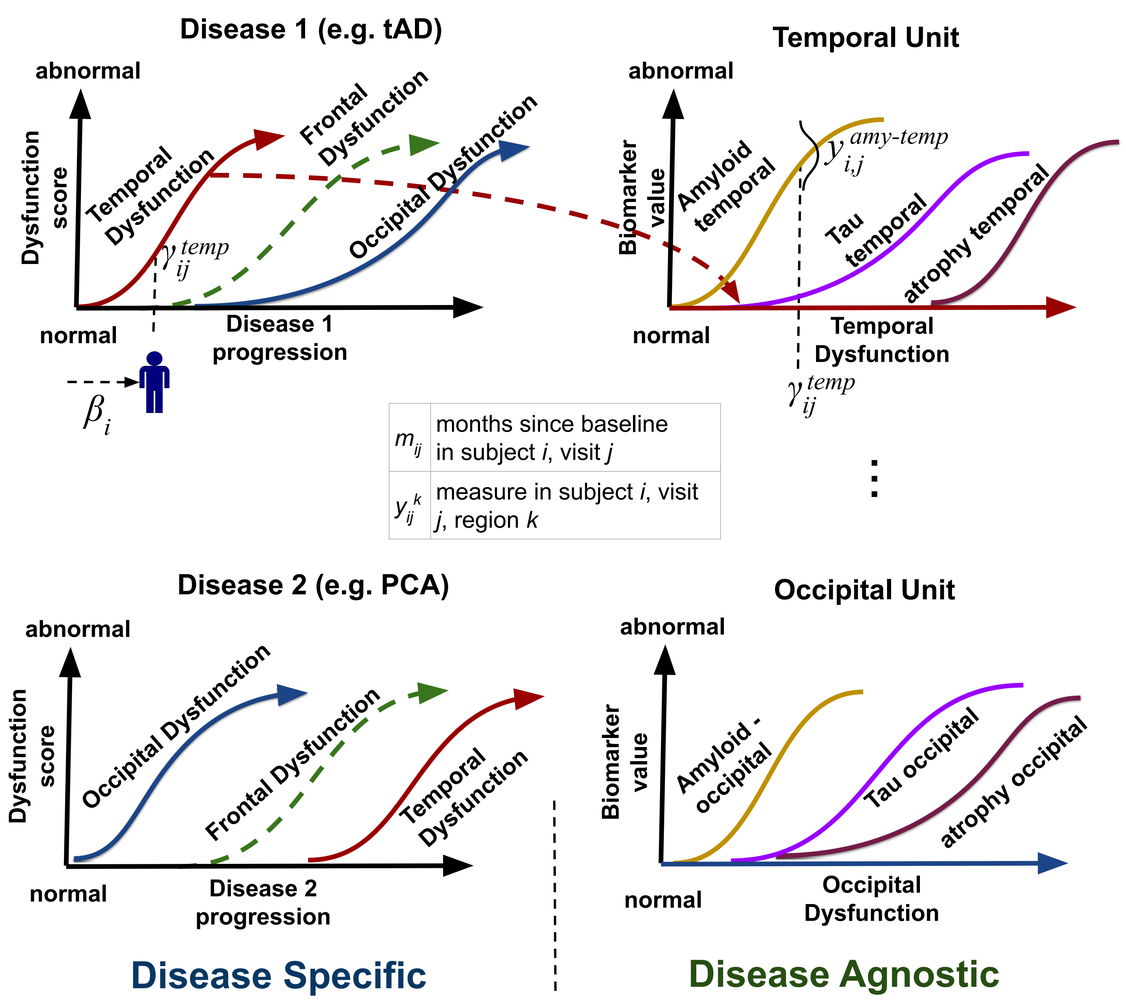
2. Method

1. Each disease characterised by region-specific dysfunction trajectories

$$\gamma_{ij}^{l} = f(\beta_i + m_{ij}; \lambda_{d_i}^{l})$$

2. Dysfunction trajectory modelled using region-specific biomarkers

$$y_{ij}^{k} = g(\gamma_{ij}^{\psi(k)}; \theta_k) + N(0, \epsilon_k)$$



m_{ij}	months since baseline in subject *i*, visit *j*
y_{ij}^{k}	measure in subject *i*, visit *j*, region *k*

3. Extend to multiple subjects, biomarkers and diseases

$$p(\mathbf{y}|\theta, \lambda, \beta, \epsilon) = \prod_{(i,j,k)\in\Omega} p(y_{ij}^{k}|\theta_k, \lambda_{d_i}^{\psi(k)}, \beta_i)$$

3. Inference with belief propagation

while θ, λ, β *not converged* **do**

; // Estimate biomarker trajectories (disease agnostic)

$$\theta_k^{(u)} = \arg\min_{\theta_k} \sum_{(i,j)\in\Omega_k} \left[y_{ij}^{k} - g\left(f(\beta_i^{(u-1)} + m_{ij}; \lambda_{d_i}^{\psi(k),(u-1)}); \theta_k \right) \right]^2$$

; // Estimate dysfunction trajectories (disease specific)

$$\lambda_d^{l,(u)} = \arg\min_{\lambda_d^{l}} \sum_{(i,j,k)\in\Omega_{d,l}} \left[y_{ij}^{k} - g\left(f(\beta_i^{(u-1)} + m_{ij}; \lambda_d^{l}); \theta_k^{(u)} \right) \right]^2$$

; // Estimate subject-specific time shifts

$$\beta_i^{(u)} = \arg\min_{\beta_i} \sum_{(j,k)\in\Omega_i} \left[y_{ij}^{k} - g\left(f(\beta_i + m_{ij}; \lambda_{d_i}^{\psi(k),(u)}); \theta_k^{(u)} \right) \right]^2$$

4. Datasets

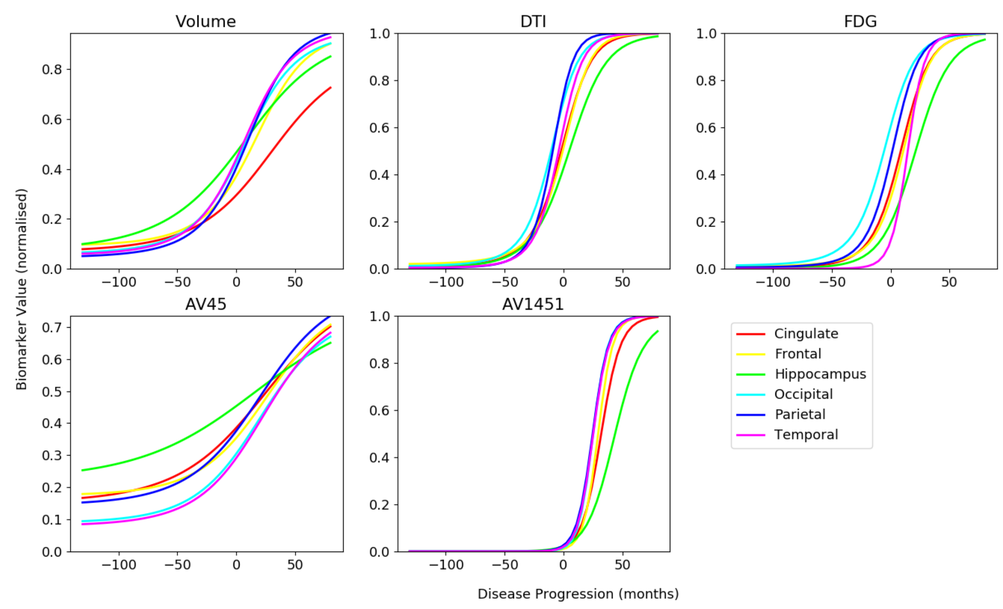
- TADPOLE dataset (ADNI) split into three subgroups with different progressions: 21 hippocampal, 35 cortical, 27 subcortical.
- Dementia Research Center cohort: MRI scans from 76 PCA, 67 tAD, 87 controls for training, 10 PCA with DTI for validation.

5. Results

- Our model has favourable performance compared to other models, on two different datasets.

Model	Cingulate	Frontal	Hippocam.	Occipital	Parietal	Temporal
	TADPOLE: Hippocampal subgroup to Cortical subgroup					
DKT (ours)	0.56 ± 0.23	**0.35 ± 0.17**	**0.58 ± 0.14**	-0.10 ± 0.29	**0.71 ± 0.11**	**0.34 ± 0.26**
AD model	0.44 ± 0.25	0.34 ± 0.21	0.34 ± 0.24*	**-0.07 ± 0.22**	0.64 ± 0.16	0.08 ± 0.24*
Multivariate	**0.60 ± 0.18**	0.11 ± 0.22*	0.12 ± 0.29*	-0.22 ± 0.22	-0.44 ± 0.14*	-0.32 ± 0.29*
Spline	-0.24 ± 0.25*	-0.06 ± 0.27*	0.58 ± 0.17	-0.16 ± 0.27	0.23 ± 0.25*	0.10 ± 0.25*
Linear	-0.24 ± 0.25*	0.20 ± 0.25*	0.58 ± 0.17	-0.16 ± 0.27	0.23 ± 0.25*	0.13 ± 0.23*
	typical Alzheimer's to Posterior Cortical Atrophy					
DKT (ours)	0.77 ± 0.11	0.39 ± 0.26	0.75 ± 0.09	0.60 ± 0.14	**0.55 ± 0.24**	**0.35 ± 0.22**
AD model	**0.80 ± 0.09**	**0.53 ± 0.17**	**0.80 ± 0.12**	0.56 ± 0.18	0.50 ± 0.21	0.32 ± 0.24
Multivariate	0.73 ± 0.09	0.45 ± 0.22	0.71 ± 0.08	-0.28 ± 0.21*	0.53 ± 0.22	0.25 ± 0.23*
Spline	0.52 ± 0.20*	-0.03 ± 0.35*	0.66 ± 0.11*	0.09 ± 0.25*	0.53 ± 0.20	0.30 ± 0.21*
Linear	0.52 ± 0.20*	0.34 ± 0.27	0.66 ± 0.11*	**0.64 ± 0.17**	0.54 ± 0.22	0.30 ± 0.21*

- Inferred multimodal trajectories for PCA in lack of such data.
- Results are plausible, suggesting late-stage posterior damage.



6. Conclusion

- Developed a novel methodology and model for transfer learning across different diseases
- Inferred multimodal trajectories for Posterior Cortical Atrophy

Weblinks

- Source code: https://github.com/mrazvan22/dkt
- Website: https://people.csail.mit.edu/razvan/

Funders

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