Bayesian Modeling of Atrophy Factors in Alzheimer's Disease

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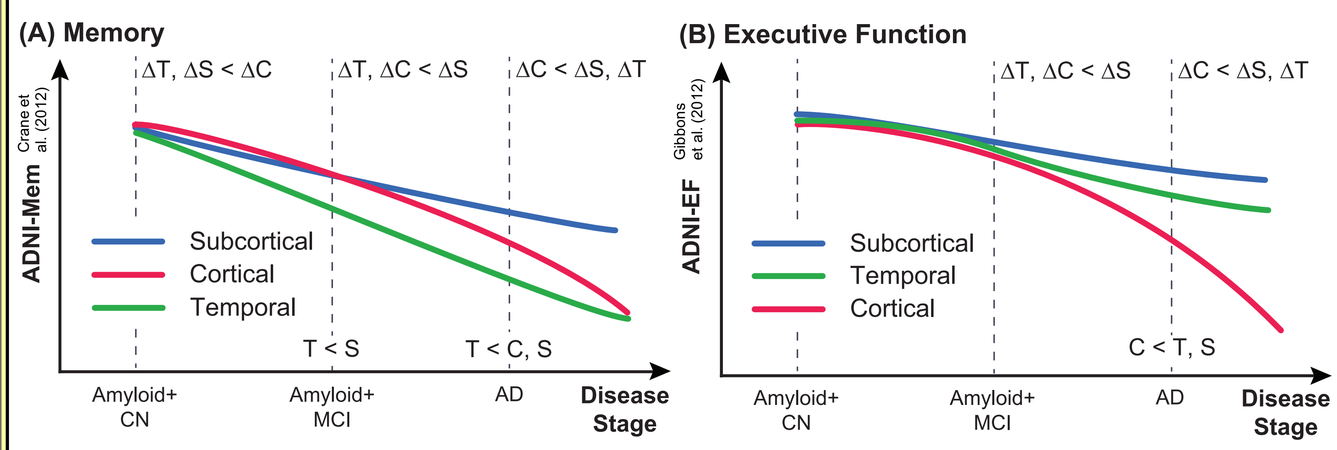
Abstract

Alzheimer's disease (AD) is the most common form of dementia. Although AD is typically associated with temporal lobe atrophy and an amnestic clinical presentation, it has become increasingly clear that heterogeneity exists within this disease. Here we employed a data-driven Bayesian model to automatically identify distinct latent factors of overlapping atrophy patterns from structural MRI data of late-onset AD patients. Our approach estimated the extent to which multiple distinct atrophy patterns were expressed within each patient rather than assuming that each patient expresses a single atrophy factor.

Our model revealed three atrophy factors: temporal, subcortical, and cortical factors. Among AD patients, temporal factor had the worst memory, while cortical factor had the worst executive function and the fastest decline rates in both memory and executive function. Next, we applied this model to amyloid-positive non-demented participants. Among amyloid-positive mild cognitively impaired (MCI) participants, temporal and cortical factors exhibited more rapid memory and executive function decline than subcortical factor. Furthermore, analyses of amyloid-positive cognitively normal (CN) participants suggested that memory trajectories diverged at the preclinical stage, where temporal factor showed faster memory decline rates than cortical factor.

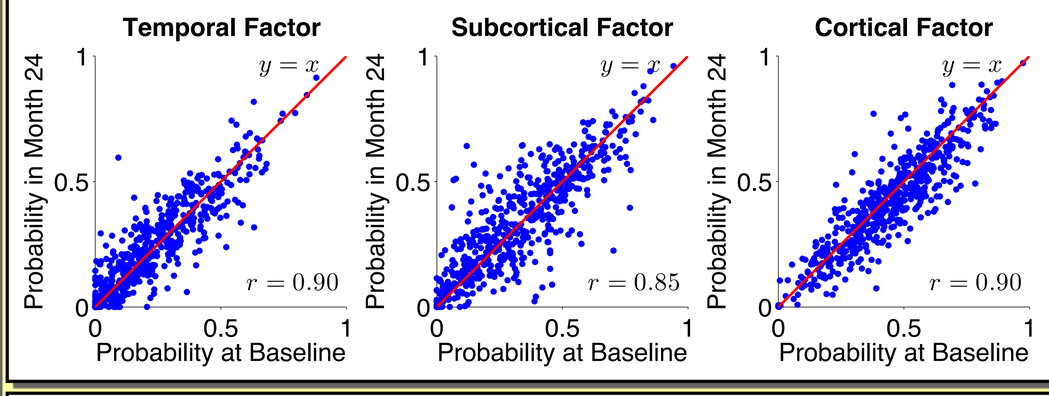
These results emphasize the presence of distinct atrophy factors linked to different cognitive domains and suggest that this heterogeneity has implications for cognitive decline trajectories. This analytic approach might potentially enable individual-level predictions relevant for prognosis and customized therapies.

Full Trajectories of Memory & Executive Functions



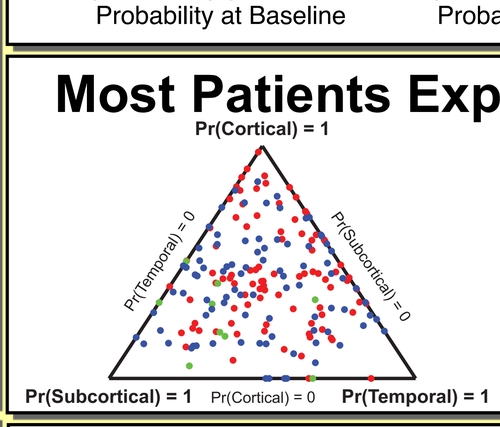
- AD affected memory earlier than executive function (regardless of factors)
- Memory trajectories diverged at asymptomatic stage, but not executive function
- Trajectories of **cortical** & **temporal** transposed between memory & executive function
- **Subcortical** mildest in both memory & executive function deterioration
- AD dementia: **temporal** had worst memory; **cortical** had worst executive function
- AD dementia: **cortical** exhibited fastest deterioration rates in both memory & executive function

Factors Are Stable Despite Disease Progression



- No systematic shift from one factor to another after two years from baseline
- Factors are NOT simply disease stages

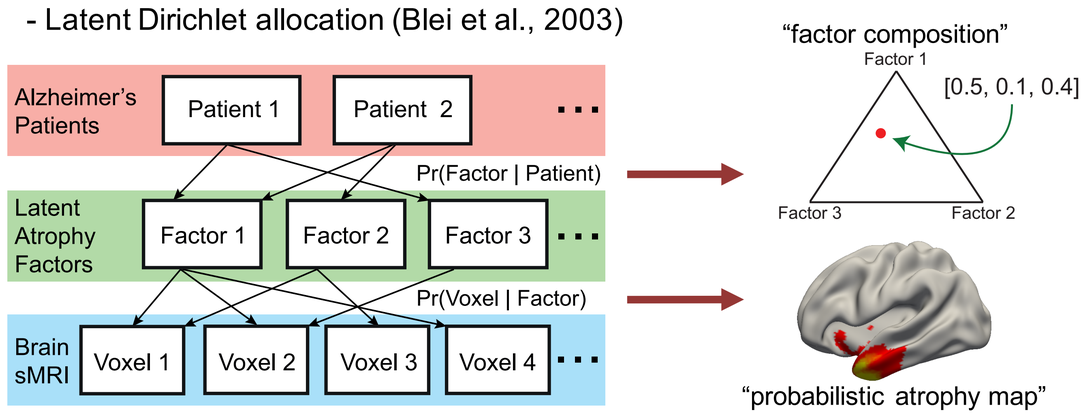
Most Patients Expressed Multiple Atrophy Factors



- Each patient is a dot; location represents factor composition; color stands for amyloid status: **amyloid-positive**, **amyloid-negative**, and **unknown**
- Most patients exhibited multiple atrophy factors (e.g., [0.6, 0.3, 0.1]; cf. previous subtype studies)

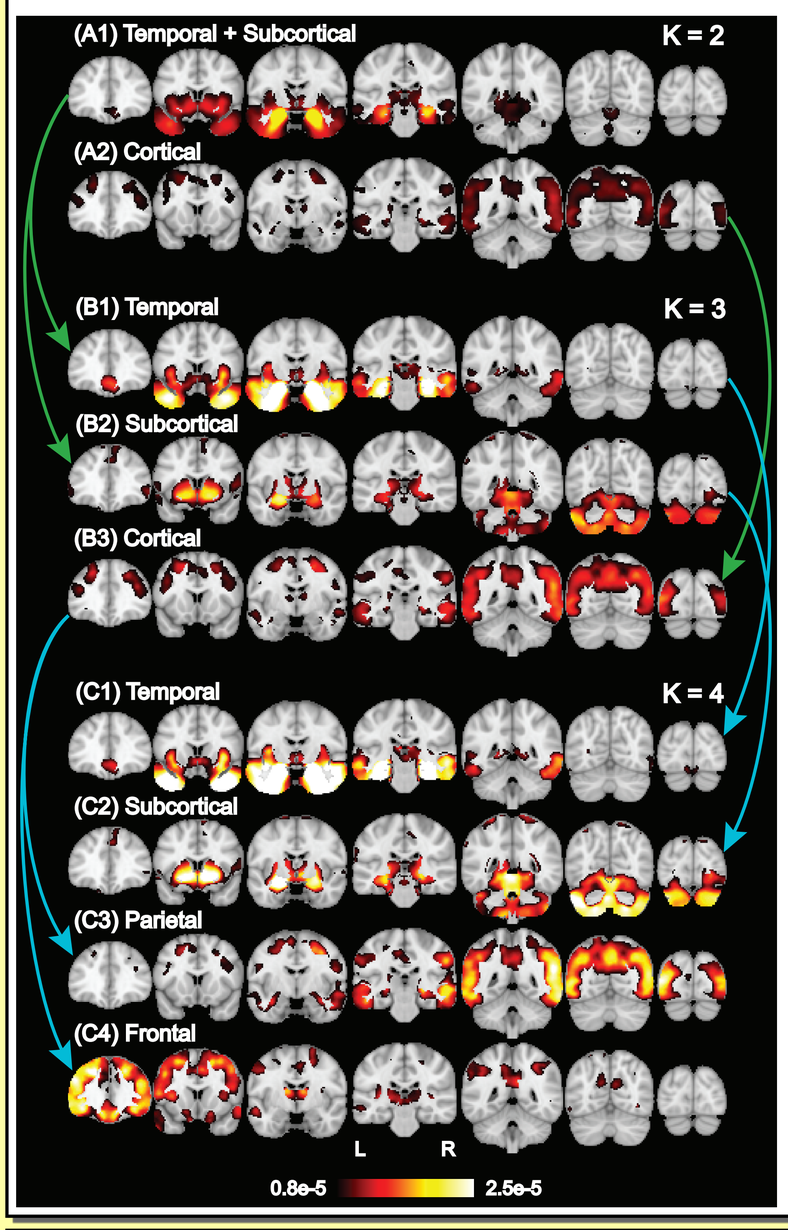
Methods

- **Stage 1: Compute voxelwise atrophy for each patient**
  - Voxel-based morphometry (Ashburner & Friston, 2000; FSL-VBM)
  - Apply $\log_{10}$, regress nuisance variables, z-scores, threshold, discretize
- **Stage 2: Estimate latent atrophy factors with AD dementia patients**
  - Latent Dirichlet allocation (Blei et al., 2003)



- **Stage 3: Infer factor compositions of amyloid-positive MCI & CN participants**
- **Stage 4: Examine trajectories of memory and executive functions**

Nested Hierarchy of Atrophy Factors



K = 2 Atrophy Factors
- **Temporal+subcortical**
- **Cortical**

K = 3 Atrophy Factors
- **Temporal**: atrophy in temporal lobe & hippocampus
- **Subcortical**: atrophy in cerebellum, striatum, & thalamus
- **Cortical**: atrophy in frontal & parietal cerebral cortices

K = 4 Atrophy Factors
- **Temporal**
- **Subcortical**
- **Parietal**
- **Frontal**

Factor-Dependent Patient Characteristics

	Temporal	Subcortical	Cortical	Overall p*
Baseline age (years)	76 (6.9)	76 (7.1)	74 (7.8)	**8e-7**
Age at AD onset (years)†	72 (7.5)	73 (7.7)	70 (8.5)	**1e-5**
Years from onset to baseline†	3.8 (2.6)	3.5 (2.4)	3.5 (2.4)	0.29
APOE ε2§	0.03 (0.2)	0.08 (0.3)	0.04 (0.2)	**0.03**
APOE ε4§	0.86 (0.7)	0.81 (0.7)	0.87 (0.7)	0.61

- No difference in years from onset to baseline
- Subcortical: higher APOE ε2

- Cortical: youngest baseline age & age at AD onset (consistent with Murray et al., 2011, Whitwell et al., 2012, Noh et al., 2014, Ossenkoppele et al., 2015)

Conclusion

- Bayesian model revealed at least three latent atrophy factors (temporal, subcortical, & cortical)
- Patients expressed multiple atrophy factors (e.g., [0.6, 0.3, 0.1])
- Memory trajectories diverged at preclinical stage: temporal & subcortical showed faster memory degradation rates than cortical
- MCI participants: temporal & cortical showed faster decline rates in both memory & executive function than subcortical
- AD dementia: temporal had worst memory; cortical had worst executive function
- AD dementia: cortical showed fastest decline rates in both memory & executive function
- Factor compositions stable despite disease progression
- Factor compositions might act as individualized factor diagnosis predicting memory & executive function decline

References

- Ashburner J, Friston KJ (2000) Voxel-based morphometry—the methods. *NeuroImage* 11(6):805-821.
- Blei DM, Ng AY, Jordan MI (2003) Latent Dirichlet allocation. *J Machine Learning Res* 3:993-1022.
- Bernal-Rusiel JL, Greve DN, Reuter M, Fischl B, Sabuncu MR (2013) Statistical analysis of longitudinal neuroimage data with linear mixed effects models. *NeuroImage* 66:249-260.
- Crane PK, et al. (2012) Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Brain Imaging Behav* 6(4):502-516.
- Gibbons LE, et al. (2012) A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment. *Brain Imaging Behav* 6(4):517-527.
- Murray ME, et al. (2011) Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. *Lancet Neurol* 10(9):785-796.
- Noh Y, et al. (2014) Anatomical heterogeneity of Alzheimer disease based on cortical thickness on MRIs. *Neurology* 83(21):1936-1944.
- Ossenkoppele R, et al. (2015) Atrophy patterns in early clinical stages across distinct phenotypes of Alzheimer's disease. *Hum Brain Map* 36(11):4421-4437.
- Whitwell JL, et al. (2012) Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: a case-control study. *Lancet Neurol* 11(10):868-877.

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