Bayesian Modeling of Atrophy Factors in Alzheimer’s Disease

Xiuming Zhang¹, Elizabeth C. Mormino², Nanbo Sun¹
Reisa A. Sperling², Mert R. Sabuncu³, 4, B.T. Thomas Yeo¹, 5

¹ASTAR-NUS CIRC, Dept of ECE, SINAPSE, NUS, Singapore; ²Dept of Neurol, MGH/HMS, USA;
³Martinos Ctr for Biomed Imag, MGH/HMS, USA; ⁴CSAIL, MIT, USA; ⁵Ctr forCog Neurosci, Duke-NUS, Singapore

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 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. 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, while 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.

Methods
- Stage 1: Compute voxelwise atrophy for each patient
  - Voxel-based morphometry (Ashburner & Friston, 2000; FSL-VBM)
  - Apply log., 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

Nest 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

Factors are stable despite disease progression
- Each patient is a dot; location represents factor composition; color: amyloid status; yellow: amyloid-positive, red: amyloid-negative, white: unknown
- Most patients exhibited multiple atrophy factors (e.g., {0.6, 0.3, 0.1}; cf. previous subtype studies)

Factor-dependent patient characteristics

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

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 prediction
- AD dementia: cortical showed fastest decline rates in both memory & executive function
- Factor compositions stable despite disease progression
- Factor compositions might act as individual factor diagnosis predicting memory & executive function decline

References

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