Effects of Baseline Regional Amyloid Deposition Patterns on Subsequent Accumulation

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Introduction

Overview

- The cortical summary (CS) SUVR of ^{18}F-AV-45 PET scans (frontal/parietal/temporal/cingulate ROI) is a conveniently calculated measure of global ß-Amyloid burden
- CS SUVR is impaired by:
  - noise introduced via choosing a reference region
  - ignorance of regional variations within the ROI
  - ignorance of regional contrasts (except ROI/ref)

Goals

- **Convert regional uptakes of ADNI ^{18}F-AV-45 and ^{18}F-AV-1451 PET scans to standardized units via a regionally-unbiased intensity normalization method**
- **Perform a sparse nonparametric factor analysis of the normalized regional dataset, determining a set of recurring uptake topographies underlying the variance in individual uptake patterns**
- **Explore the efficacy of topographical factor scores (derived from the factor model) as alternative summary measures of Alzheimer's disease severity**

Subjects

	ADNI ^{18}F-AV-45	ADNI ^{18}F-AV-1451
n	1064	55
Age (yrs)	73.77 (7.48)	76.04 (6.98)
Sex (M/F)	569/494 (1 N/A)	31/24
Education (yrs)	16.21 (2.67)	16.72 (2.65)
APOE ε4 +	43.2%	34.5%
AV45 +	52.6%	N/A
Normal	259 (24.3%)	17 (30.9%)
SMC	100 (9.4%)	6 (10.9%)
EMCI	301 (28.2%)	11 (20%)
LMCI	215 (20.2%)	16 (29.1%)
AD	189 (17.7%)	5 (9.1%)

Methods

Data Normalization

- 45 bilateral Freesurfer-defined regions
- Correction for partial volume effects with the Rousset algorithm (geometry-dependent transfer matrix)
- Intensity normalization by Manhattan (L1) norm, mapping each scan (row) onto a regional standard simplex and preserving uptake ratios
- Standardize each region (column) to zero mean, unit variance

Freesurfer Regions

$$X = \begin{bmatrix} x_{11} & x_{12} & x_{13} & \cdots & x_{1D} \\ x_{21} & x_{22} & x_{23} & \cdots & x_{2D} \\ x_{31} & x_{32} & x_{33} & \cdots & x_{3D} \\ \vdots & \vdots & \vdots & & \vdots \\ x_{N1} & x_{N2} & x_{N3} & \cdots & x_{ND} \end{bmatrix} \text{ Scans}$$

Nonparametric Sparse Factor Analysis (NSFA)

- Sparsity improves interpretability of latent factors and downstream predictive performance
- Nonparametric models remove manual specification of the number of factors
- Potential pitfalls include the assumption of a linear causal model, and the results are only as good as the data

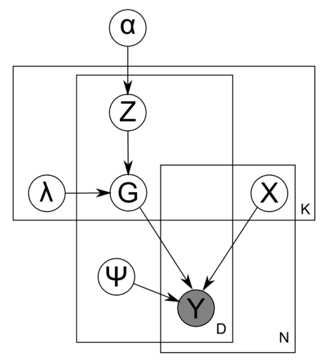


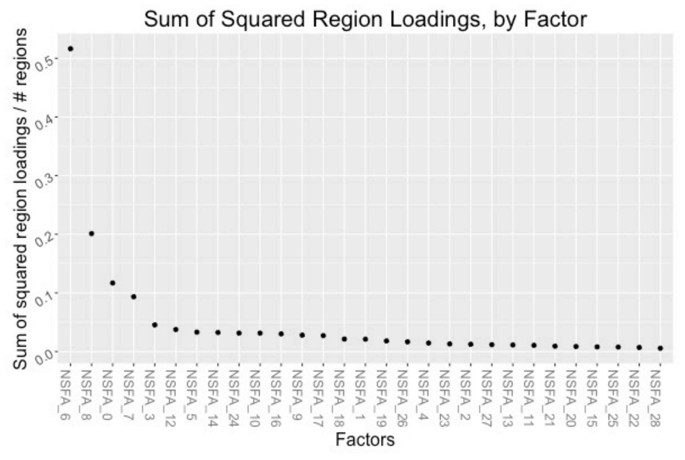
Figure 1. Graphical Model. Adapted from "Nonparametric Bayesian sparse factor models with application to gene expression modeling" by D. Knowles and Z. Ghahramani, 2011

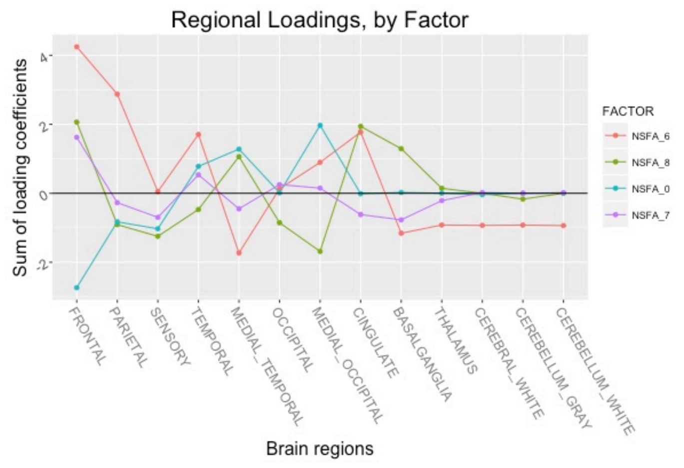
NSFA Output and Analyses

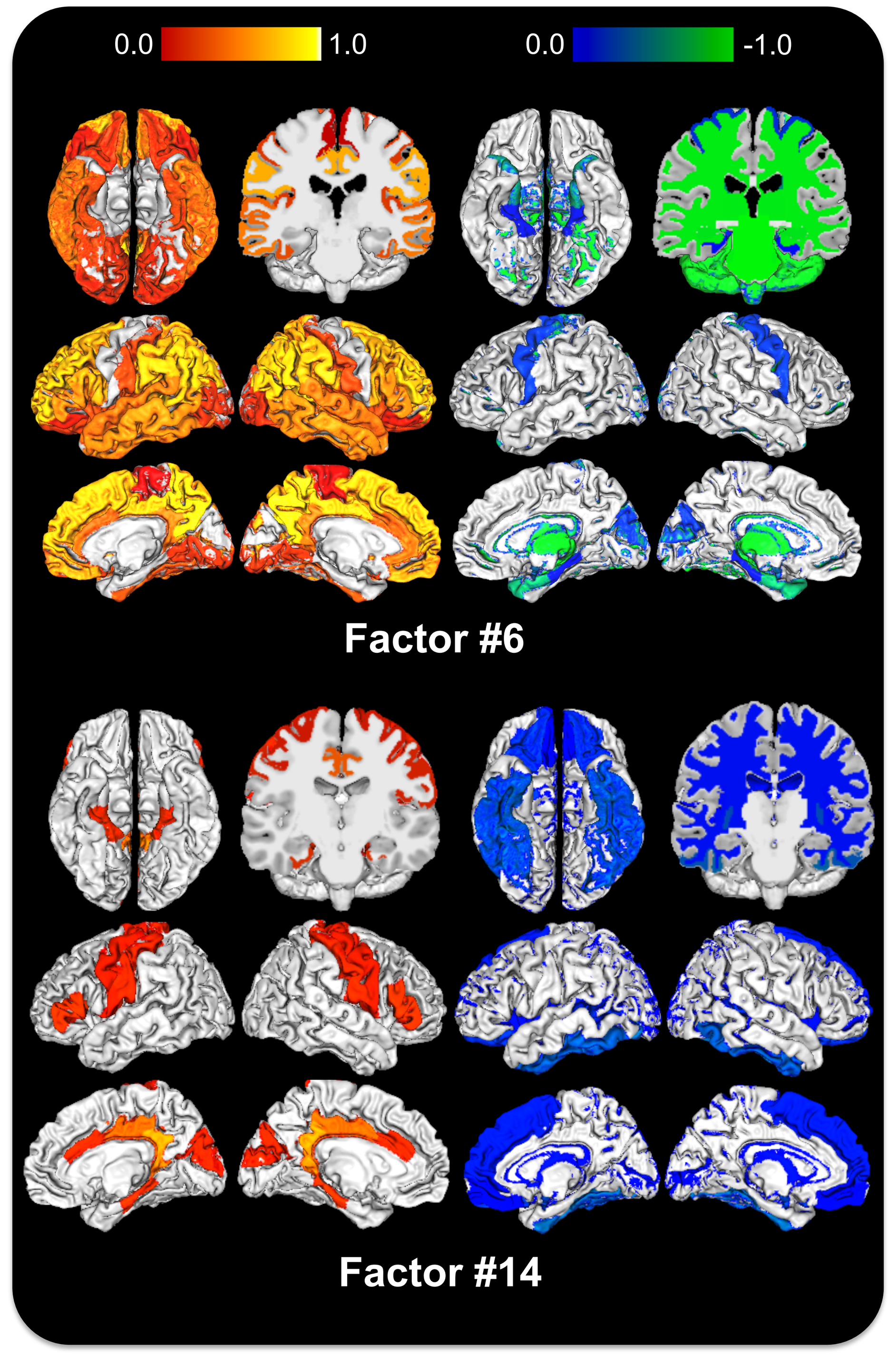
- Factor loadings (regional topographies per factor)
  - Loadings are regional correlations
  - Summary by lobe
  - Overlap with de facto ROIs
- Factor score estimates (factor representations per scan)
  - Correlation with cortical summary SUVR
  - Longitudinal behavior
  - Penalized linear regression models (LARS) targeting cognition and annualized change in global burden
    - Covariates: Age, Sex, Edu (yrs), APOE ε4 status
    - Test model performance with 10-fold cross validation

Results and Summary

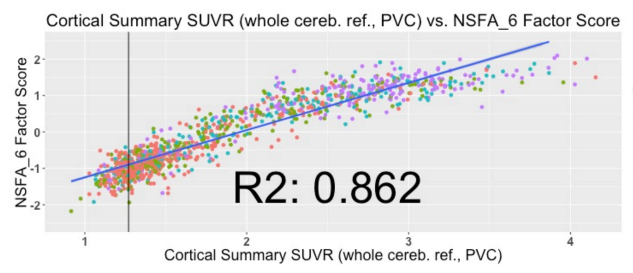
^{18}F-AV-45 Factor Loadings (29 Factors)





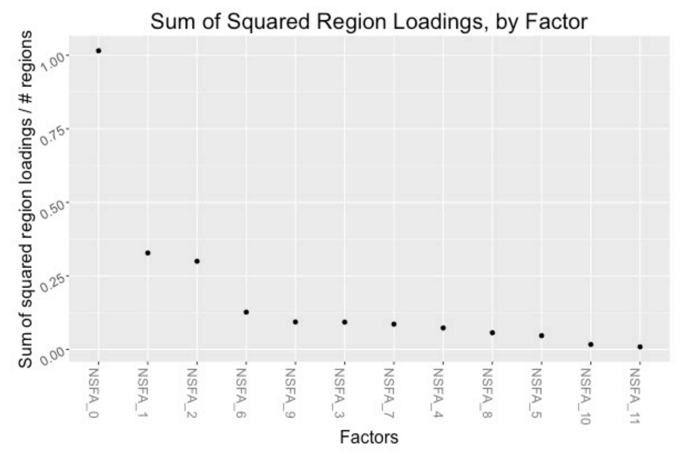


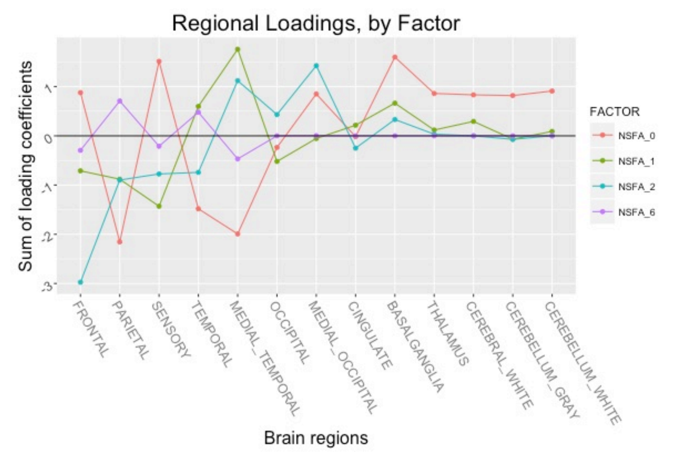
Factor #6 Score vs. CS SUVR

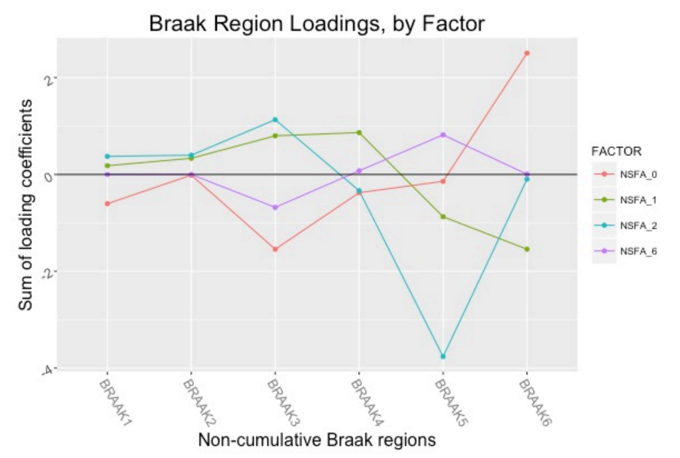


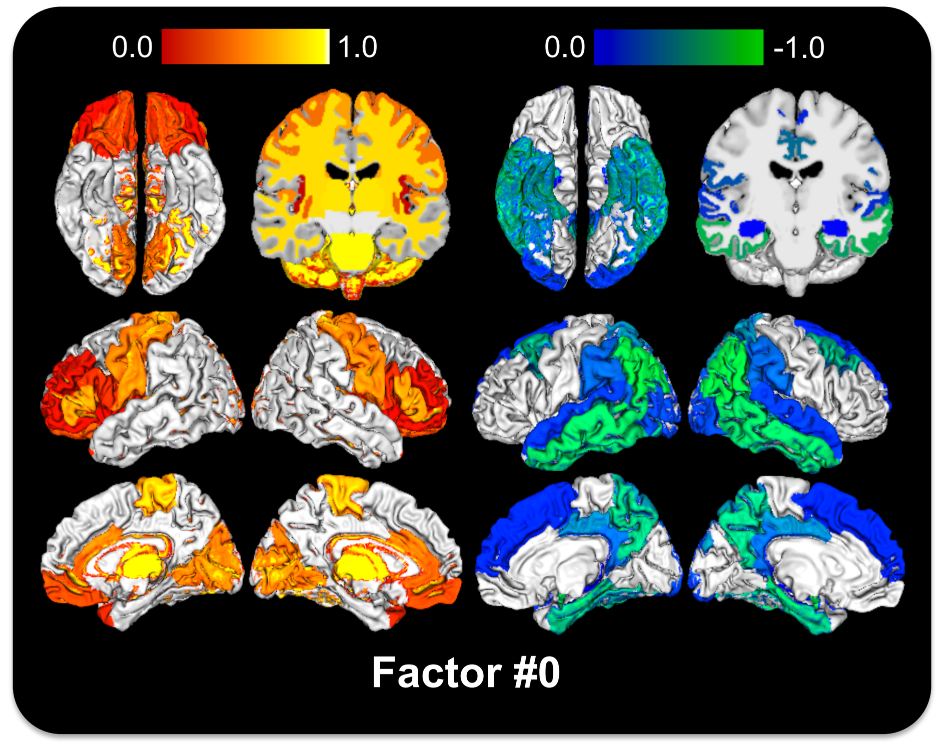
^{18}F-AV-45 LARS Results	CS change (Factors, n=616)	CS change (CS SUVR, n=616)	ADAS-Cog (Factors, n=516)	ADAS-Cog (CS SUVR, n=516)
Significant predictors	**#6**: ** β=0.016, p=3e-9	**CS SUVR**: *** β=0.021, p=3e-4 **APOE ε4**: *** β=0.015, p=5e-3	**#6**: *** β=5.43, p<2e-16 **#14**: *** β=-1.86, p=3e-7	**CS SUVR**: *** β=8.98, p<2e-16
R^2	0.055	0.059	0.19	0.17
Adj. R^2	0.054	0.056	0.19	0.17
R^2 Shrinkage	0.048	0.045	0.18	0.16
Likelihood ratio test	F = 35.9, p<3e-9 ***	F = 19.2, p<8e-9 ***	F = 60.1, p<2.2e-16 ***	F = 107.7, p<2.2e-16 ***

^{18}F-AV-1451 Factor Loadings (12 Factors)









^{18}F-AV-1451 LARS Results	ADAS-Cog (Factors, n=60)	ADAS-Cog (Braak SUVR, n=60)
Significant predictors	**#0**: *** β=-4.6, p<6e-11 **#9**: β=0.92, p=0.3	**Braak V**: *** β=29.2, p=8e-4 **Braak III**: β=-5.5, p=0.47
R^2	0.53	0.34
Adj. R^2	0.52	0.32
R^2 Shrinkage	0.40	0.08
Likelihood ratio test	F = 32.4, p<4e-10 ***	F = 14.9, p<6e-6 ***

Summary

- The predominant ^{18}F-AV-45 factor (#6) is very similar to cortical summary SUVR, and outperforms CS SUVR in correlation with cross-sectional cognition amongst florbetapir positive subjects
- A ^{18}F-AV-45 factor (#14) tracks variation between the cingulate and frontal/inferior temporal regions, providing additional predictive power for cross sectional cognition
- A ^{18}F-AV-1451 factor (#0) outperforms all Braak region SUVRs in correlation with cross-sectional cognition
- Results encourage further investigation of inter-modal factor associations, the value of factor scores as longitudinal measures, and a voxel-wise factor analysis