



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 β -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 an alternative summary measure 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 $\epsilon 4$ +	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 maps each scan (row) onto a regional standard simplex and preserves uptake ratios
- Standardize each region (column) to zero mean, unit variance

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

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
- G is the matrix of factor loadings
- X is the matrix of independent hidden factors
- Ψ is Gaussian noise

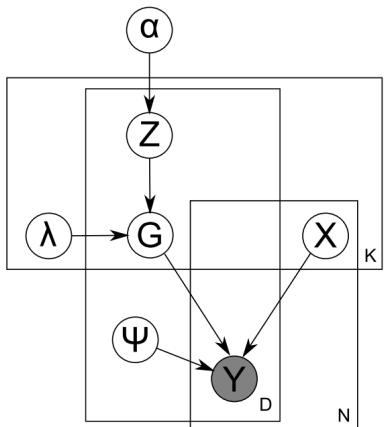


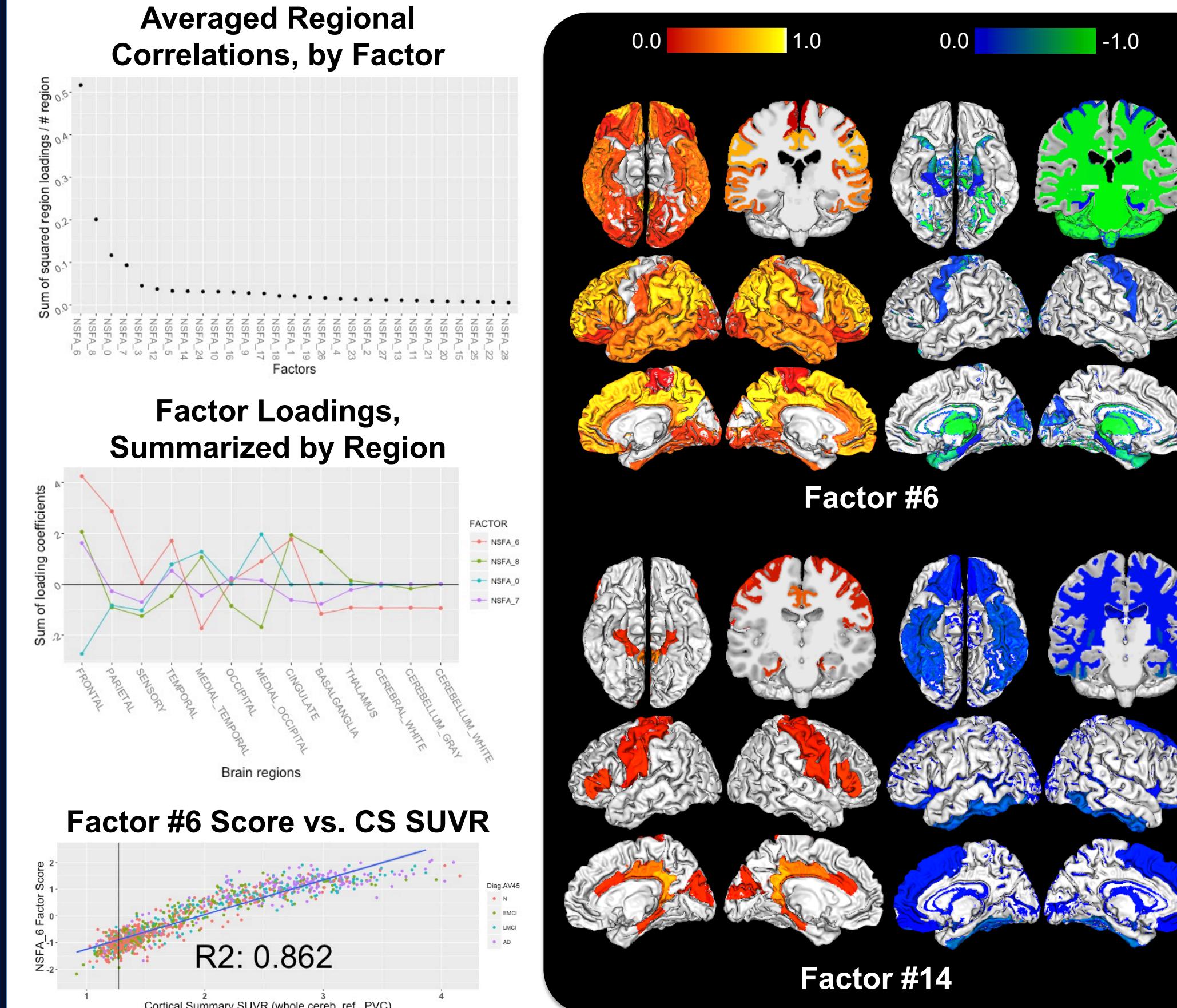
Figure 1. Graphical Model. Adapted from "Nonparametric Bayesian sparse factor models with application to gene expression modeling" by D. Knowles and Z. Ghahramani, 2011

NSFA Output and Analyses

- Factor loadings (regional topographies per factor)
 - Loadings as 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 $\epsilon 4$ status
 - Test model performance with 10-fold cross validation

Results and Summary

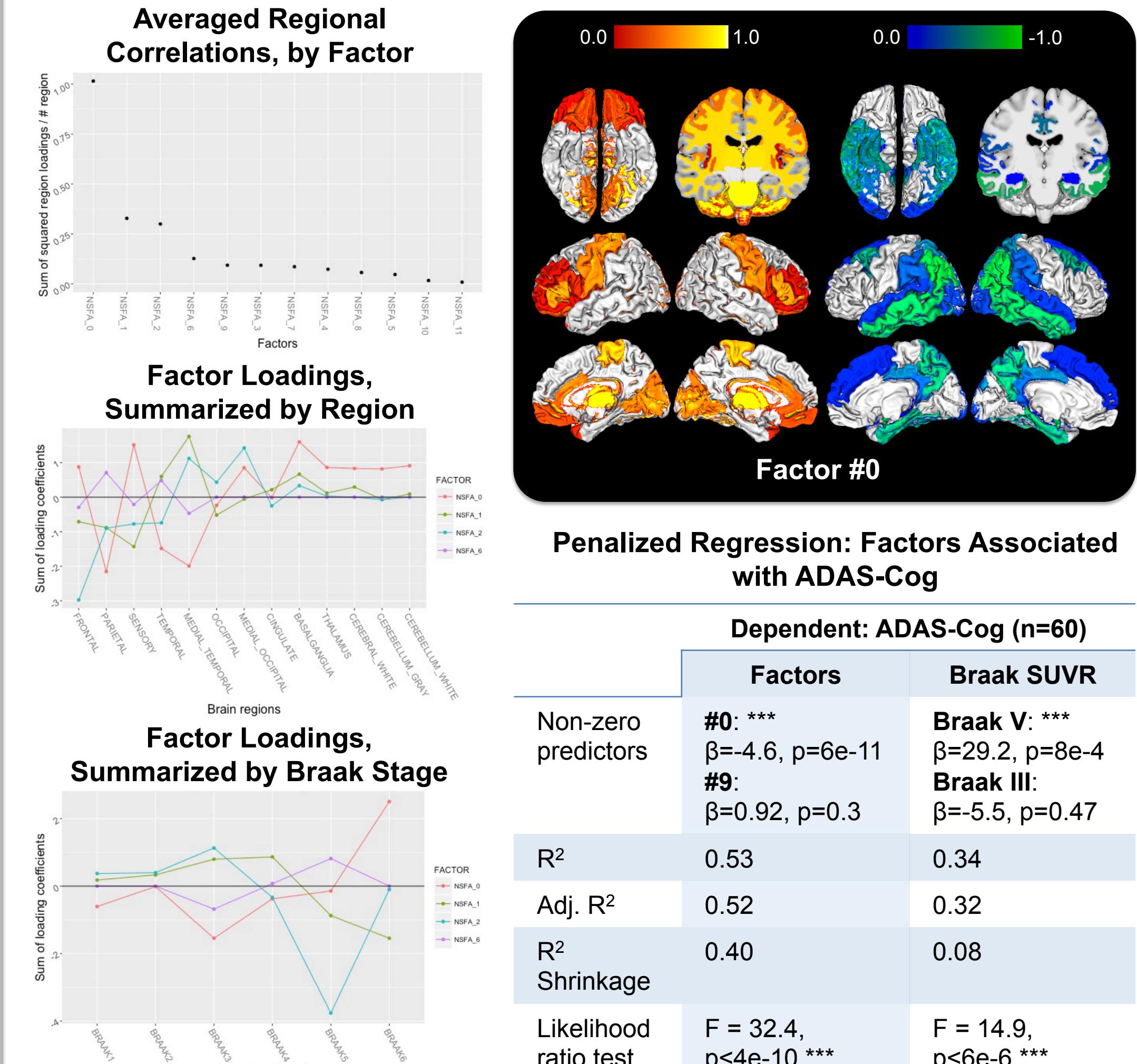
Amyloid Deposition Topography Factors (29 Factors)



Penalized Regression: Factors Associated with Amyloid Change & ADAS-cog

	Dependent: CS change (n=616)	Dependent: ADAS-cog (n=516, AV45+)		
	Factors	CS SUVR	Factors	CS SUVR
Non-zero predictors	#6: ** $\beta=0.016, p=3e-9$	CS SUVR: *** $\beta=0.021, p=3e-4$	#6: *** $\beta=5.43, p<2e-16$	CS SUVR: *** $\beta=8.98, p<2e-16$
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 ***

Tau Deposition Topography Factors (12 Factors)



Summary

- The predominant ^{18}F -AV-45 factor (#6) recapitulates cortical summary SUVR in regional topography and its relationships to longitudinal amyloid deposition and ADAS-cog amongst florbetapir positive subjects
- A ^{18}F -AV-45 factor (#14) tracks variation between the cingulate and frontal/inferior temporal regions, providing predictive power for ADAS-cog beyond the cortical summary SUVR
- A ^{18}F -AV-1451 factor (#0) outperforms all Braak region SUVRs in relation with ADAS-cog
- Results encourage further investigation of inter-modal factor associations, the value of factor scores as longitudinal measures, and a voxel-wise factor analysis