Cerebral Small Vessel Disease in Early HIV Infection
Multimodal imaging findings

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Background – the dataset

- Chicago Early HIV Infection Study (ACE) - unique dataset that includes comprehensive neuroimaging, neurocognitive and blood measures in participants with mean infection duration of 1 year
  - Advanced neuroimaging protocol probing multiple aspects of brain health including structure, microstructure, spontaneous brain activity, iron deposition, and myelination etc.
- Participants recruited between 2008-2014 for baseline and two-year follow-up visits
  - Includes subgroups of infection duration <4mos, 4-12mos, >12mos
  - approximately equal numbers of cART naïve and cART-initiated PLWH

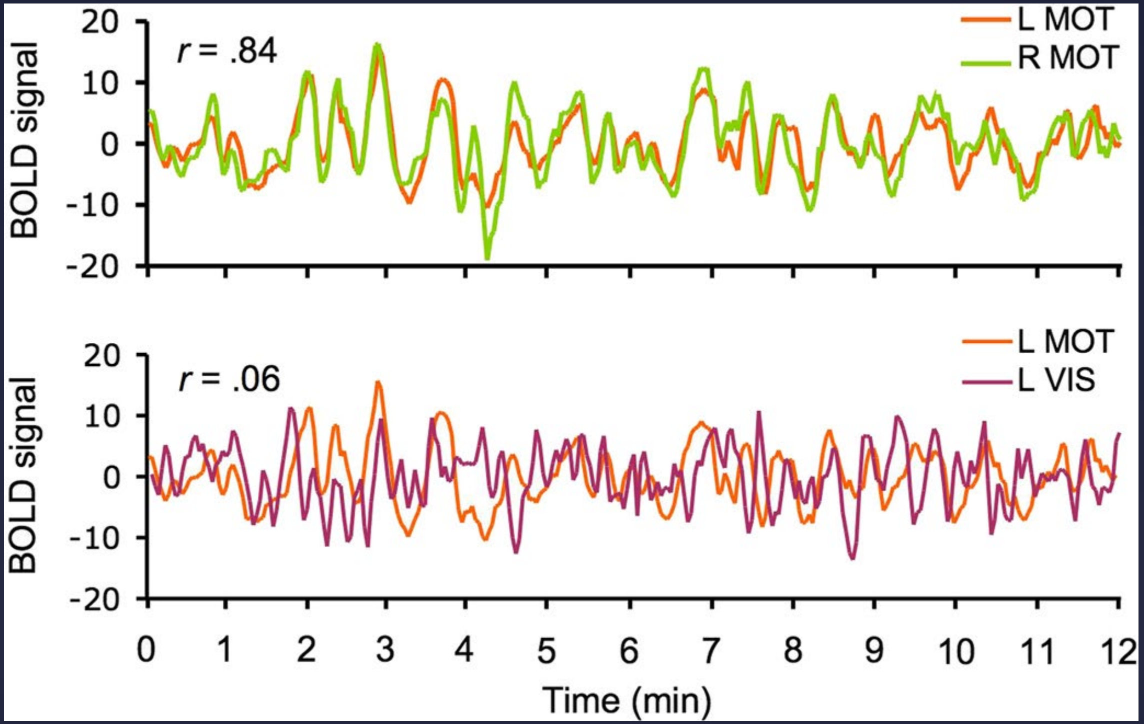
Background – motivation

- Prior ACE imaging findings identified abnormalities in regions susceptible to cerebral small vessel disease(CSVD) – basal ganglia, thalamus, cerebellum etc. (Ragin et al. Neurology. 2012; 79(24): 2328, Kelly et al. J Neurovirol. 2014 Oct;20(5):514, Wang et al. Brain Connect. 2011;1(3):207)
- New analysis techniques developed since the original study may reveal new insight
  - The brain as a complex network
  - Fusion of multimodal data

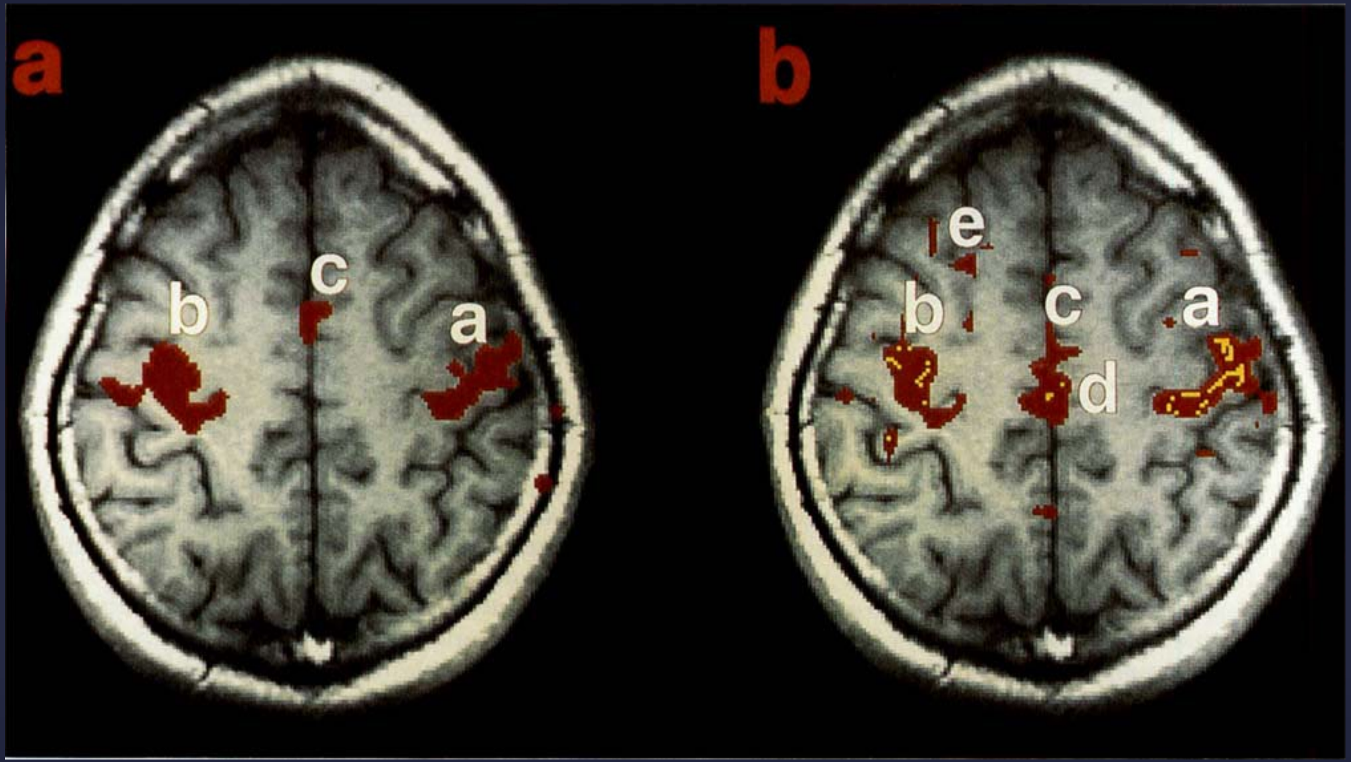
Graph Theory Analysis of RS-fMRI

Presented at Conference on Retroviruses & Opportunistic Infections 2023

Resting State fMRI (RS-fMRI)



Van Dijk, J Neurophysiol 103: 297–321, 2010



Biswal, MRM 34:537-541, 1995

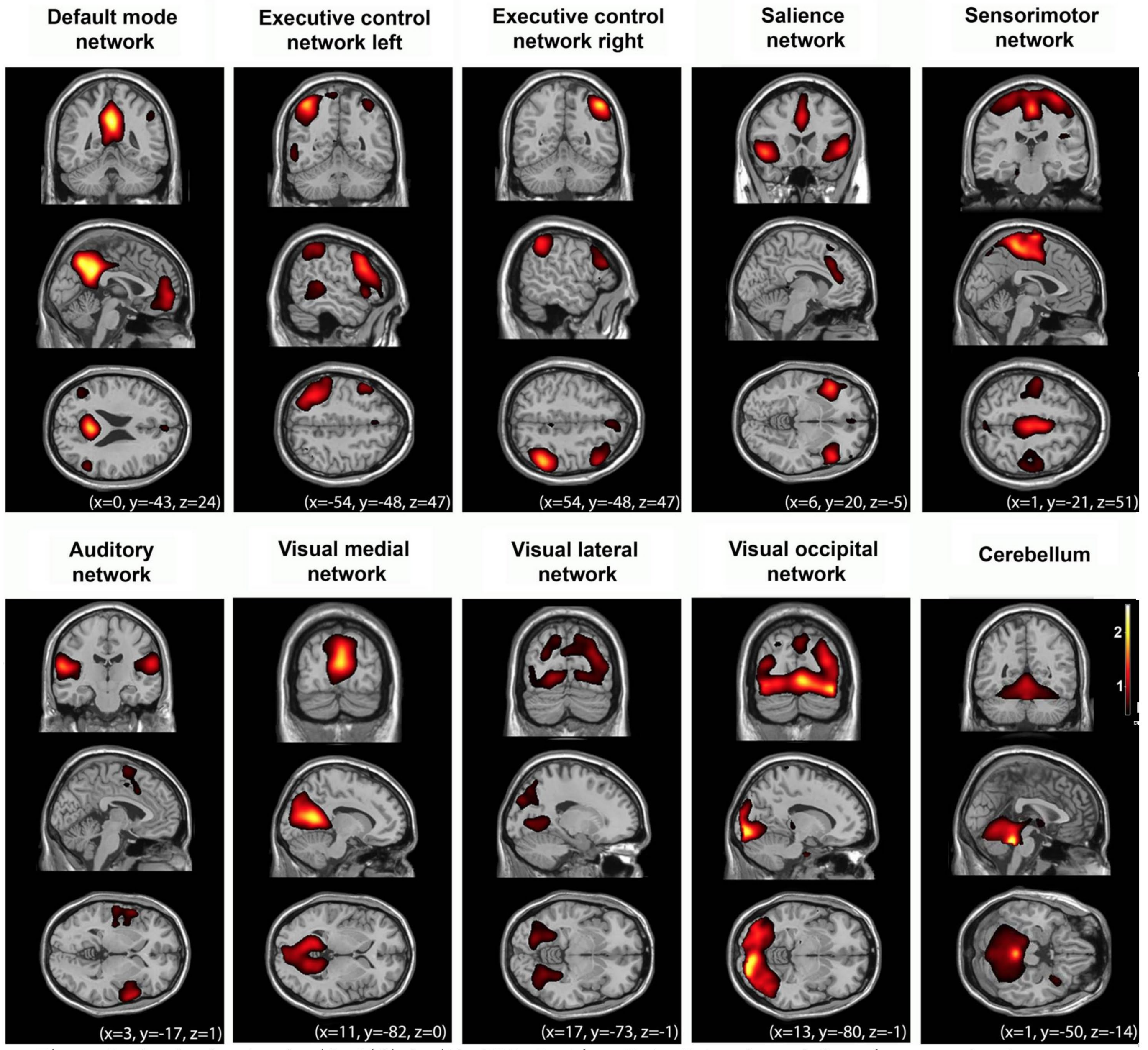
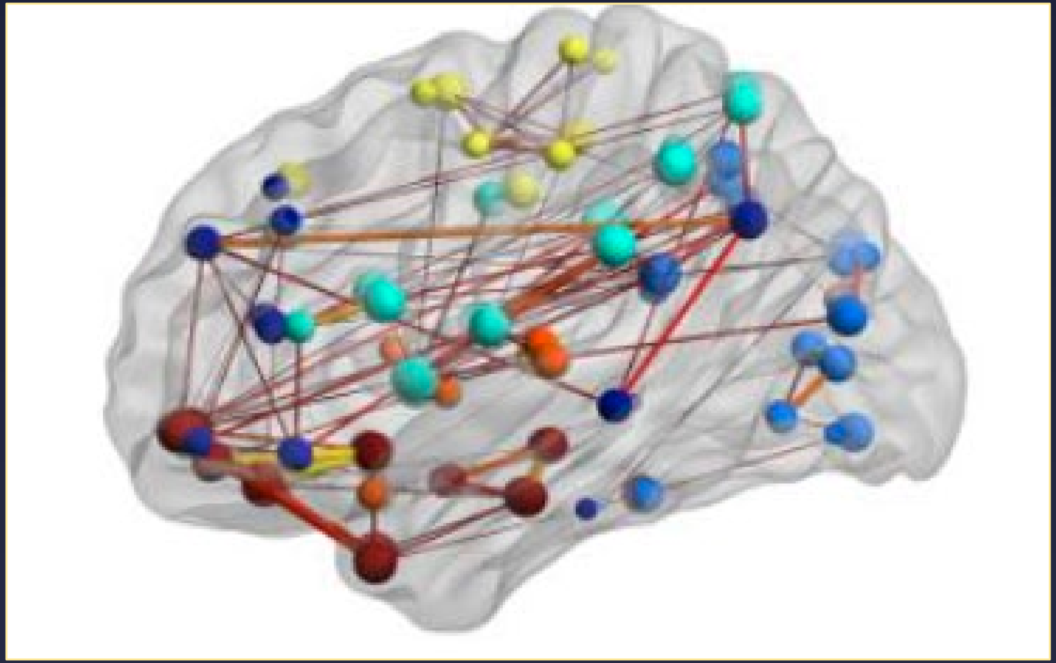


Figure 1. Cerebral networks identified with fMRI. ***Resting State Networks and Consciousness*** *(2012)*
Lizette Heine, Andrea Soddu, Francisco Gómez, Audrey Vanhaudenhuyse, Luaba Tshibanda, Marie Thonnard, Vanessa Charland-Verville, Murielle Kirsch, Steven Laureys, and Athena Demertzi doi:10.3389/fpsyg.2012.00295

Graph Theory for fMRI



Courtesy of Guixiang Ma

- Models the brain as networks of:
  - Nodes: brain regions (e.g. putamen)
  - Edges: correlations between different regions
- Graph theory metrics measure how networks are organized

Graph Theory Metrics

- Clustering Coefficient

$$C = \frac{1}{n}\sum_{i\in N} C_i = \frac{1}{n}\sum_{i\in N} \frac{2t_i}{k_i(k_i-1)},$$

where C_i is the clustering coefficient of node i ($C_i = 0$ for $k_i < 2$).

- Path Length

$$L = \frac{1}{n}\sum_{i\in N} L_i = \frac{1}{n}\sum_{i\in N} \frac{\sum_{j\in N, j\neq i} d_{ij}}{n-1},$$

where L_i is the average distance between node i and all other nodes.

- Strength

$$k_i = \sum_{j\in N} a_{ij}$$

- Global Efficiency

$$E = \frac{1}{n}\sum_{i\in N} E_i = \frac{1}{n}\sum_{i\in N} \frac{\sum_{j\in N, j\neq i} d_{ij}^{-1}}{n-1},$$

where E_i is the efficiency of node i.

- Modularity

$$Q = \sum_{u\in M}\left[e_{uu} - \left(\sum_{v\in M} e_{uv}\right)^2\right],$$

where the network is fully subdivided into a set of nonoverlapping modules M, and e_{uv} is the proportion of all links that connect nodes in module u with nodes in module v.

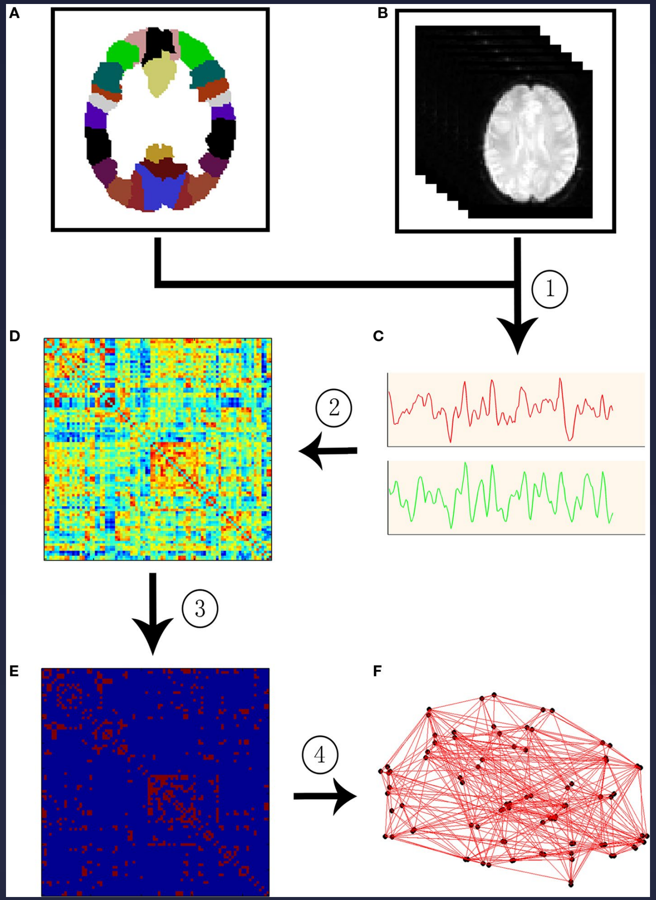
- Assortativity

$$r = \frac{l^{-1}\sum_{(i,j)\in L} k_i k_j - \left[l^{-1}\sum_{(i,j)\in L}\frac{1}{2}\left(k_i + k_j\right)\right]^2}{l^{-1}\sum_{(i,j)\in L}\frac{1}{2}\left(k_i^2 + k_j^2\right) - \left[l^{-1}\sum_{(i,j)\in L}\frac{1}{2}\left(k_i + k_j\right)\right]^2}$$

Rubinov, Mikail, and Olaf Sporns. Neuroimage 52, no. 3 (2010): 1059-1069.

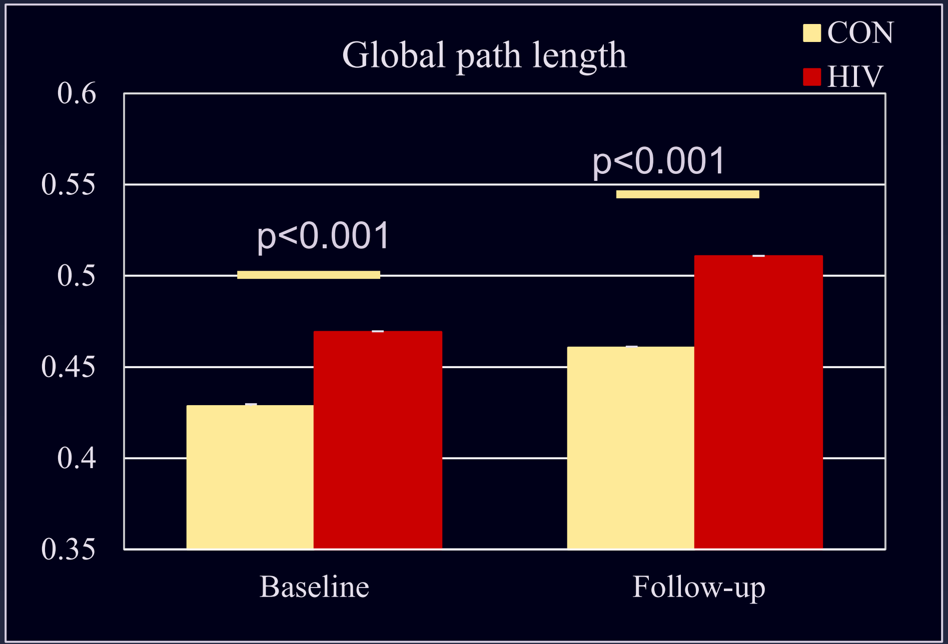
Data analysis (Guixiang Ma)

- Brain divided into 116 regions of interest(ROIs) based on AAL atlas
- Extract ROI timecourses to construct functional connectivity matrix
- Threshold connectivity matrix
- Calculate graph theory metrics
- Compared global metrics between groups using t-test
- Recursive feature elimination to identify top group-discriminating nodes (ChenYW, LinCJ. Feature Extraction: Foundations and Applications.2006; 315-324.)



Wang et al. Front. Syst. Neurosci., (2010) **4**:16

Results



Top 5 group-discriminating brain regions based on path length at both timepoints.	
Baseline	Two-year follow-up
1. Occipital_Inf_R	1. Parietal_Sup_L
2. Temporal_Sup_R	2. Cingulum_Mid_R
3. Cingulum_Mid_R	3. Vermis_7
4. Temporal_Inf_R	4. Temporal_Pole_Mid_R
5. Lingual_R	5. Frontal_Mid_Orb_L

Summary

- Global path length longer in HIV group at both timepoints
  - Path length=shortest distance between nodes
  - Measure of network integration
- Top 5 group discriminating regions changed over time
  - suggests network reorganization

Multi-modal Fusion Analysis

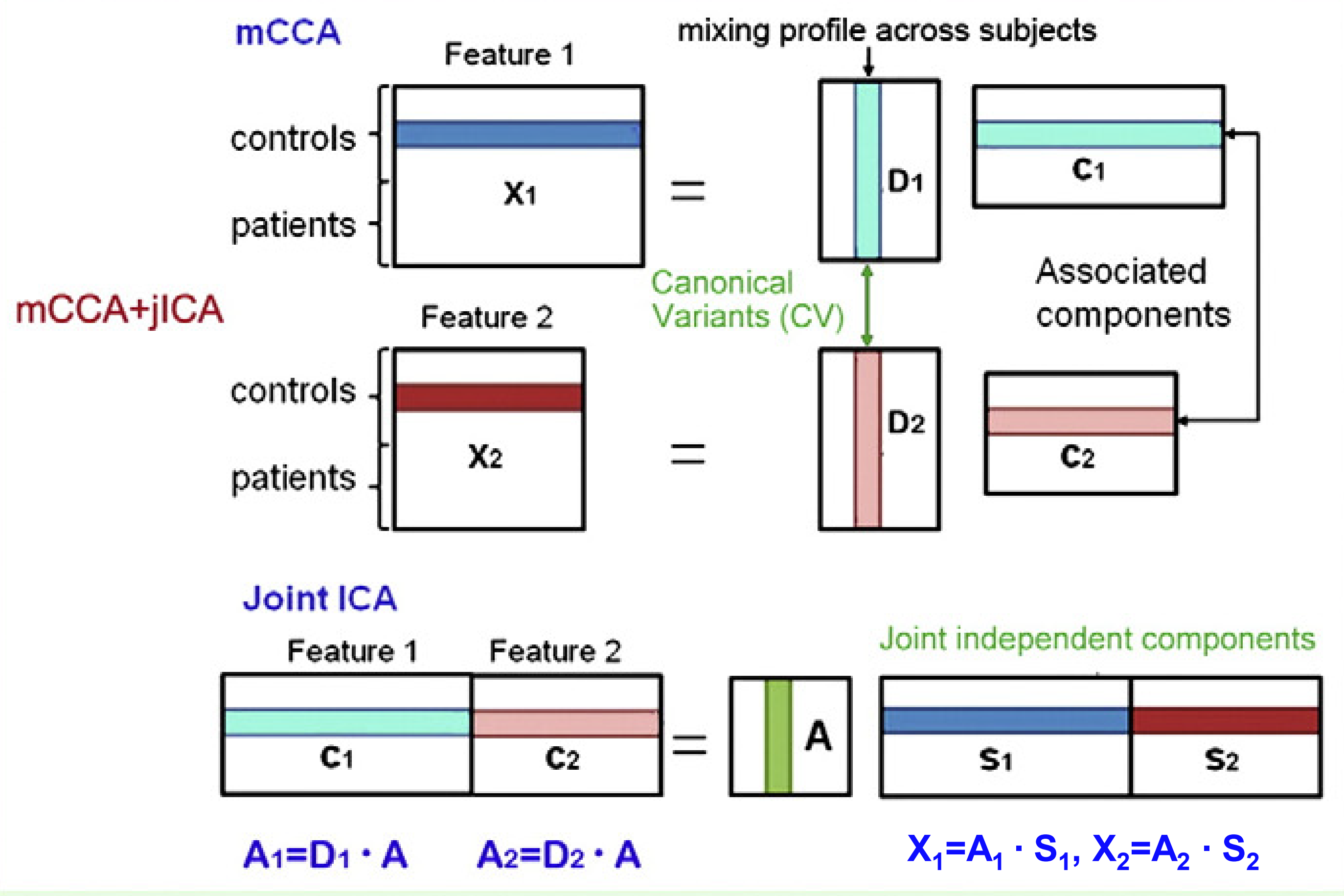
Presented at Organization for Human Brain Mapping Meeting 2023

Why data fusion?

- Traditional MRI analysis treat each dataset independently, then overlay the results
  - E.g. fMRI-brain activity, sMRI-tissue health, dMRI-white matter tract integrity
  - Does not inform about interaction between modalities
- Fusion analysis may improve sensitivity to distinguish diseased states
- More relevant today as technological advances allow collection of multiple data types within an experimental session

mCCA+jICA

- mCCA (multimodal canonical correlation analysis) – allows different mixing profile for each modality
  - Components may not be maximally distinct
- jICA (joint independent component analysis) – assumes same mixing coefficient between features but maximized spatial independence of components
- Combining both can be applied to more than 2 modalities and performs better than either one alone in simulations (Sui et al., 2012)
- Can be extended to more than 2 modalities



J. Sui et al. / NeuroImage 57 (2011) 839–855

Participants & Methods

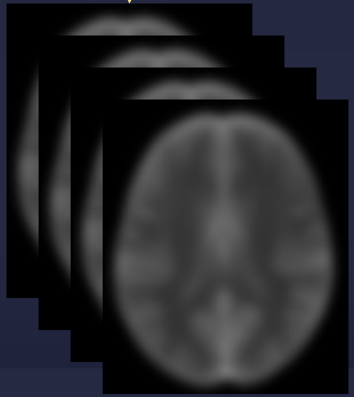
- Anatomical T1w images – tissue volume/health
- Diffusion images – white matter integrity/structural connectivity
- Resting state images – spontaneous brain activity

	Baseline		Follow-up (26.8 ± 10 months)	
	HIV+	CON	HIV+	CON
N (after image QC)	45 (20 ART)	17	41	16
Gender, m/f	42/3	14/3	38/3	14/2
Age, mean ± SD	33 ± 11	31 ± 8	33 ± 10	32 ± 9
Plasma HIV RNA ($\log_{10}$ copies/mL)	3.5 ± 1.48			
CD4+ cell count (cells/μL)	579.4 ± 244.2			

Data preprocessing (Ajay Kurani & James Higgins)

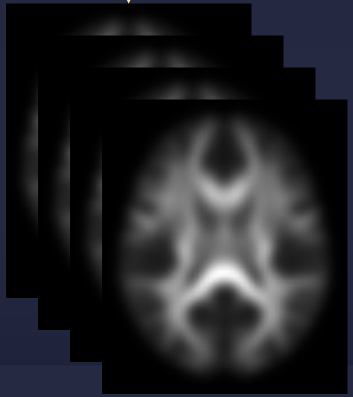
Resting state images

1. Motion correct
2. Normalize to template space
3. Bandpass filter 0.01-0.08Hz
4. Regress out motion
5. Calculate ALFF
6. Smooth by 8mm FWHM



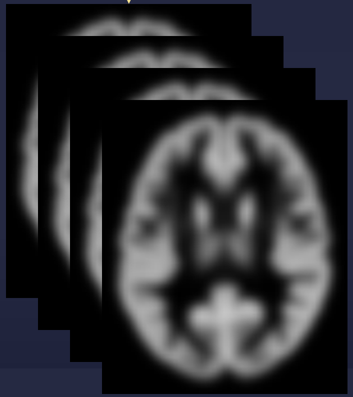
Diffusion weighted images

1. Denoise
2. Correct of motion, distortion & eddy current effects
3. Normalize to template space
4. Calculate FA
5. Smooth by 8mm FWHM



T1 weighted images

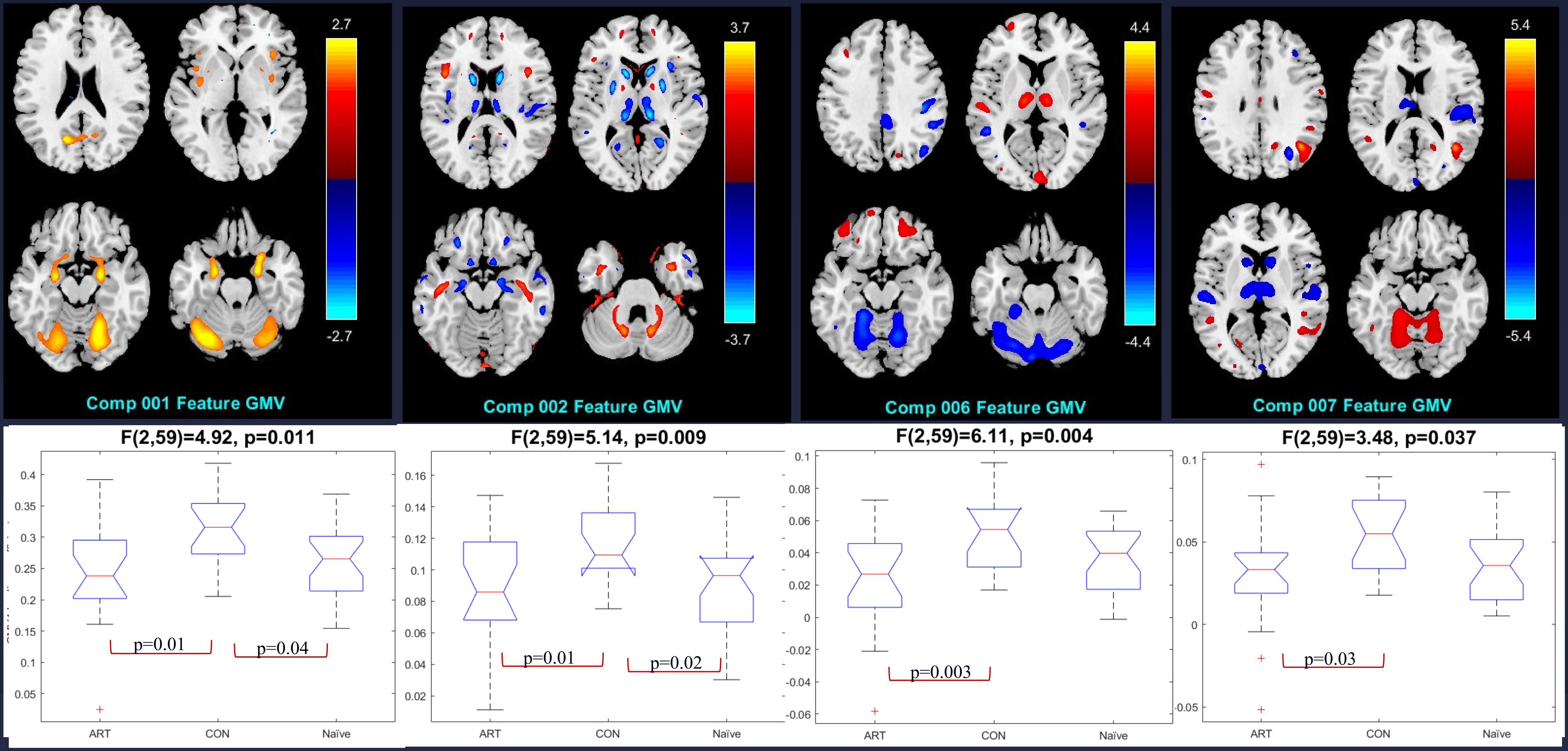
1. Segment into GM, WM , CSF
2. Dartel normalization to template space
3. Smooth by 8mm FWHM



Data fusion

- Estimate number of components for each modality
- Calculate loading coefficient of each component for each participant
- Compare loading coefficients using t-test at both timepoints to identify group-discriminating components
- Correlate loading coefficients to clinical & neuropsych. measures

Baseline Group Discriminating Components



Baseline Correlations To Clinical Measures & Age-Adjusted Neuropsych. Scores

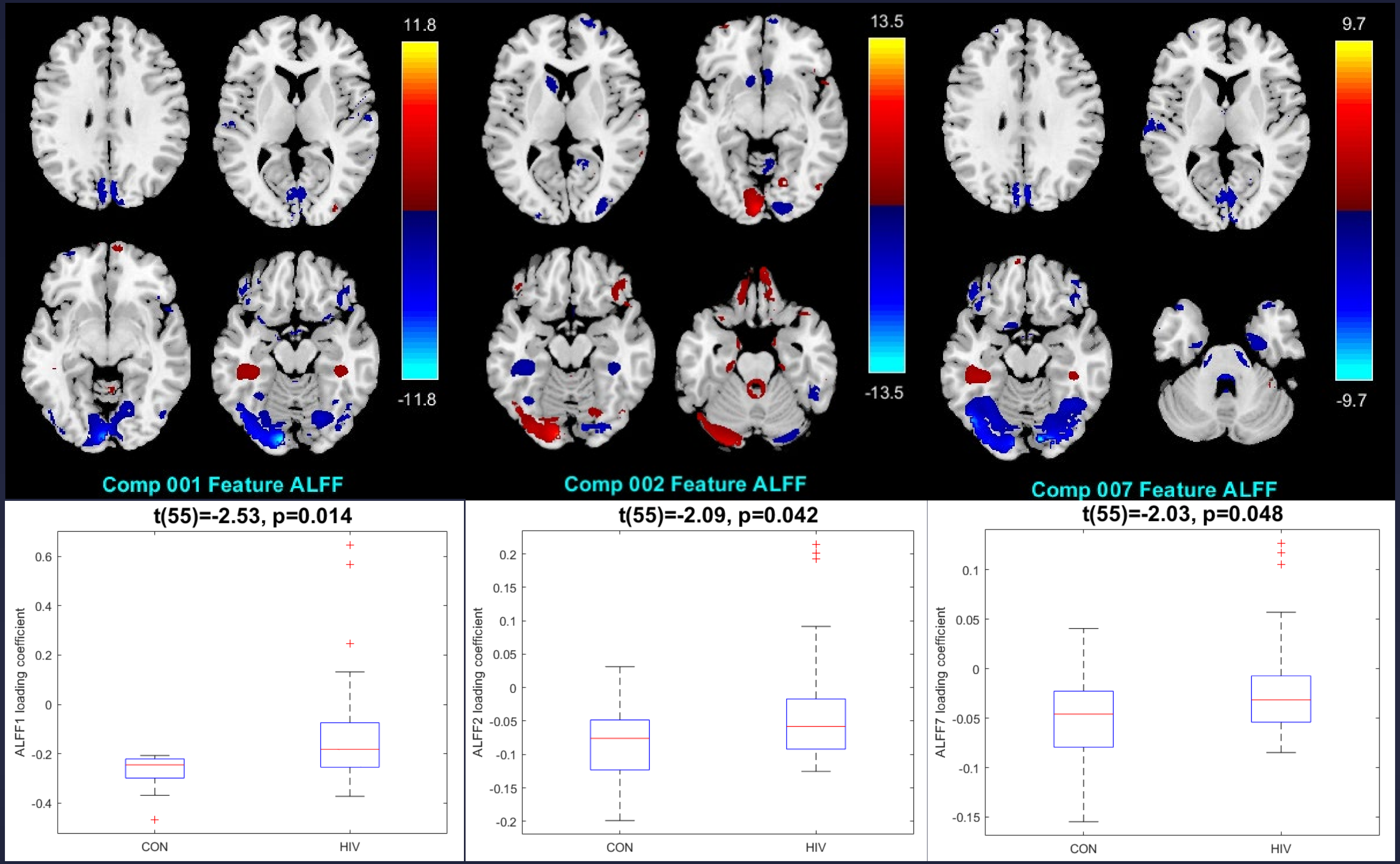
N=45	CD4 nadir	CD4/CD8 ratio	Plasma HIV RNA	CD4+ cell count	Hemoglobin
GMV1	**0.42***	0.14	0.07	**0.43***	-0.08
GMV2	**0.37**	0.22	-0.05	**0.43***	-0.17
GMV6	**0.36**	0.15	0.01	**0.38**	-0.11
GMV7	**0.45***	0.20	-0.08	**0.44***	-0.07

*p<0.005

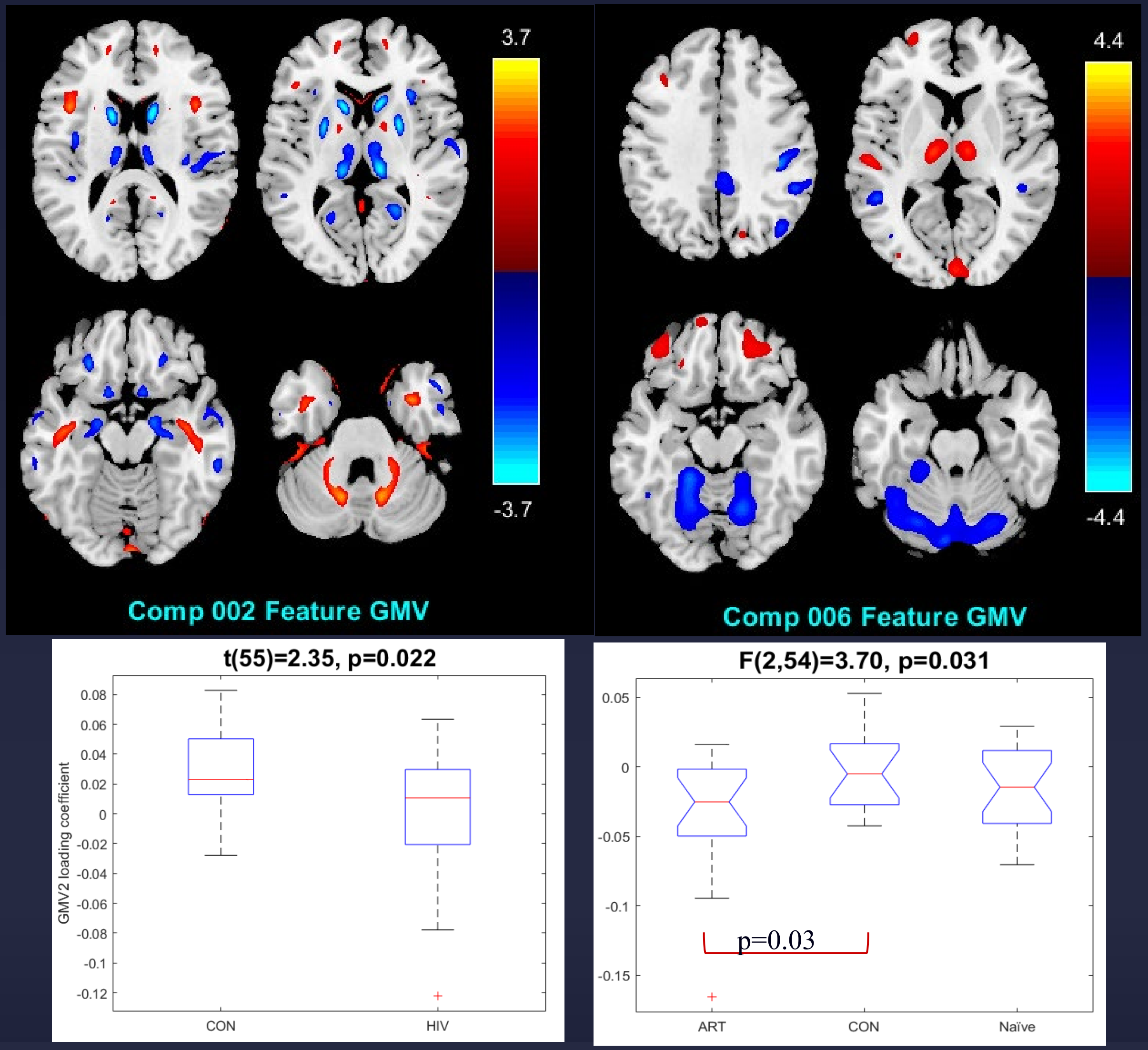
Domain	Verbal memory	Visual memory	Psychomotor	Motor speed		Executive Function		
N=62 Test	**ReyAVL. ave**	**Rey FigRecall**	**DigitSymbol**	**GPdom**	**GPnondom**	**Verbal-Fluency**	**LetterNum seq**	**OMO**
GMV1	0.04	0.06	**0.30**	-0.01	-0.06	-0.06	-0.107	-0.094
GMV2	0.17	0.04	**0.32**	-0.12	-0.08	-0.08	-0.022	-0.041
GMV6	0.14	0.09	**0.36***	-0.11	-0.12	-0.06	0.019	-0.075
GMV7	0.13	0.13	**0.28**	-0.11	-0.160	-0.08	-0.035	0.058

Prakash et al., J. Neurovirol. (2017) 23:273

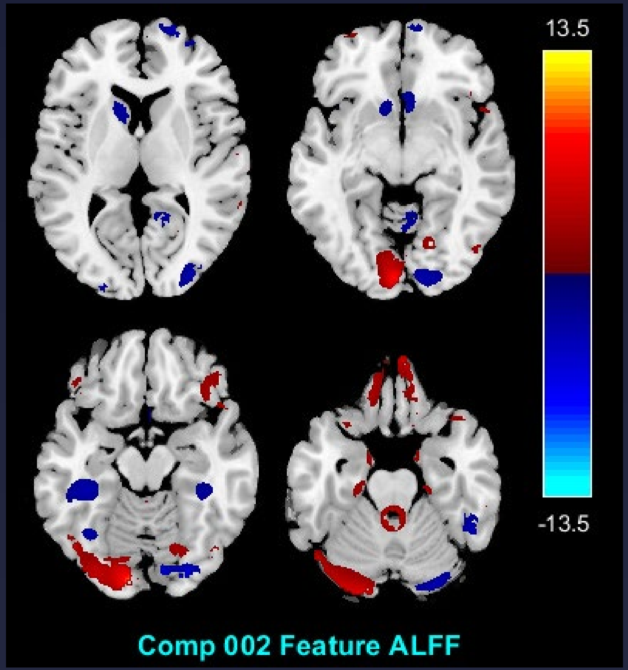
Follow-up Group Discriminating Components-ALFF

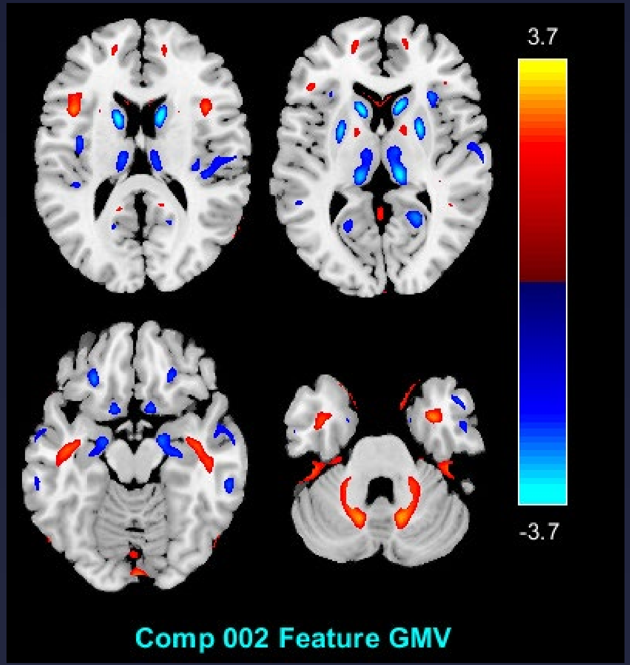


Follow-up Group Discriminating Components-GMV



Linked components





- r=-0.34, p=0.0002
- Components share same index – evidence for interaction between modalities

Follow-up Correlations With Clinical Measures & Age-Adjusted Neuropsych. Scores

N=41	**CD4 nadir**	**CD4/CD8 ratio**	**Plasma HIV RNA**	**CD4+ cell count**	**Hemoglobin**
ALFF1	0.08	0.00	-0.05	0.03	-0.14
ALFF2	0.08	0.03	-0.03	0.04	-0.17
ALFF7	0.08	0.03	-0.06	0.04	-0.15
GMV2	0.28	0.07	0.14	0.19	-0.12
GMV6	**0.39**	0.12	0.21	0.28	-0.06

Domain	Verbal memory	Visual memory	Psychomotor	Motor speed		Executive Function		
N=57 Test	**ReyAVL. ave**	**Rey FigRecall**	**DigitSymbol**	**GPdom**	**GPnondom**	**Verbal-Fluency**	**LetterNum seq**	**OMO**
ALFF1	-0.11	0.16	**-0.33**	0.02	0.04	-0.10	-0.093	-0.089
ALFF2	-0.04	0.20	-0.23	-0.05	-0.03	-0.03	-0.033	0.048
ALFF7	0.07	0.17	-0.23	-0.09	0.04	0.06	-0.052	0.112
GMV2	-0.001	**-0.28**	0.06	0.05	0.10	-0.06	-0.238	-0.142
GMV6	-0.10	-0.24	0.18	0.06	0.16	-0.07	-0.144	-0.177

Overall summary

- Graph theory analysis showed decreased network efficiency at both timepoints in HIV
- Top group discriminating nodes changed over time, indicative of network reorganization
- Fusion analysis identified structural components at baseline and functional components at follow-up that distinguished between HIV & CON.
- Expression of these networks were associated with neurocognitive performance and CD4 nadir.

Future Directions

- Construct advanced model to link these identified brain measures to behavioral & blood measures.
- Currently collecting 10 year follow-up in ACE study participants with MRI measures tailored to query vasculopathy.
  - Relate early multimodal neuroimaging findings to long-term vascular outcome.

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