Neuroimaging of HIV-Related CNS Complications for Non-Experts

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June 13, 2014

7th International Symposium on Neuropsychiatry and HIV
Barcelona, Spain

Neuroimaging of HIV Associated Neurocognitive Disorders (HAND) for Experts

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Disclosure of Interest

National Institute of Nursing Research (NINR) (R01NR012657, R01NR012907, R01NR014449)

National Institute of Mental Health (NIMH) (R21MH099979)

WUSTL Institute for Clinical and Translational Science (ICTS)

Alzheimer's Association New Investigator in Research Grant (NIRG)

WUSTL Center Women's Infectious Disease Research Pilot Grant (cWIDR)

Clinical Trials

National Institute of Aging (NIA) (RC2AG036535)- Alzheimer's Disease Neuroimaging Initiative (ADNI)
Avid Pharmaceuticals

Consultant

None

Speakers Bureau

None

I own no stocks or equity in any pharmaceutical company

Outline of Talk

- **Introduction:** To understand the pathophysiology of HIV associated neurocognitive disorders **(HAND)**
- **Methods:** To evaluate advanced neuroimaging methods for assessing HAND
- **Results:** To evaluate the effects of HIV, co-morbidities, aging, and highly active anti-retroviral therapy (HAART) in the brain using advanced neuroimaging.
- **Future:** 1) Timelines for biomarkers of HAND 2) Multi-center neuroimaging of HAND

“Doc, I Am Getting More Forgetful”

- A 64 year old Caucasian male presents with mild cognitive changes over the past few years.
- For the past 2-3 years he has noted mild memory issues including: infrequently getting lost, sometimes misplacing objects (i.e. car keys), and occasionally missing appointments.
- Friends have noticed he sometimes repeats words during a conversation and cannot remember names of certain friends (“on the top on my tongue”).

“Doc, I Am Getting More Forgetful”- Part 2

Past Medical History: HIV (diagnosed in 1988), PCP (1990), Hepatitis C (1990), drug abuse (1980’s), and neuropathy (1994), elevated cholesterol

No known family history of similar symptoms

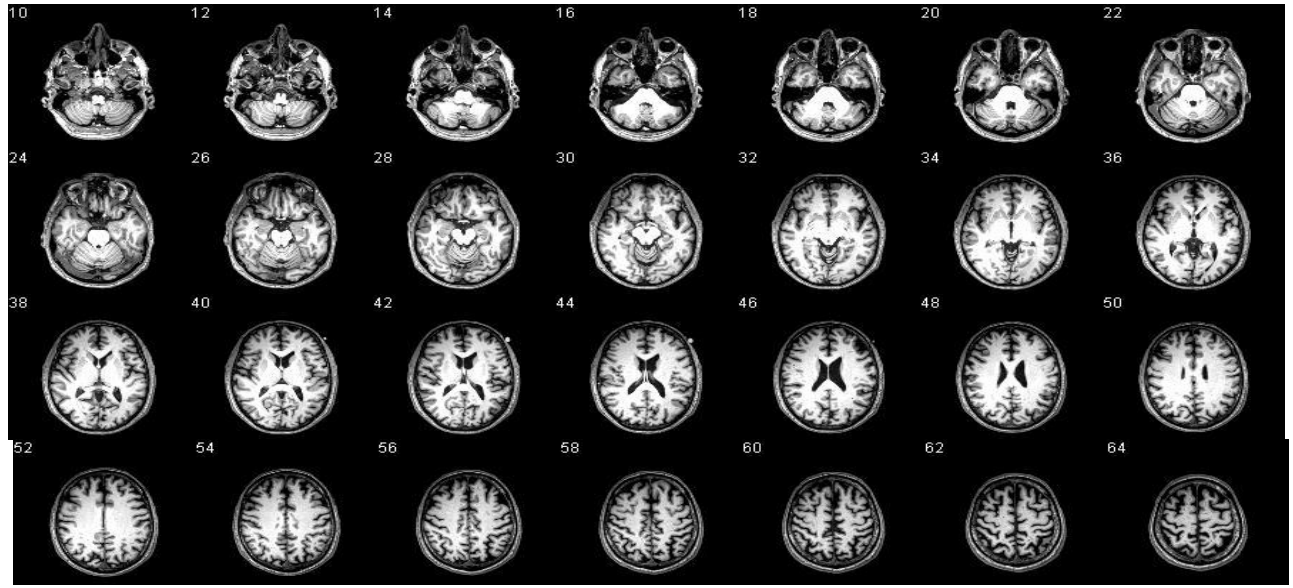
Meds: Atripla (has been on numerous HAART regimens in the past), Neurontin, and Lipitor

Exam:

Mental Status: 2/3 recall, 26 on MMSE, 24 on MoCA
Cranial nerves: 2-12 intact
Motor: Normal tone and bulk, 5/5 throughout
Sensory: Diminished sensation below the knees
Reflexes; 2+ upper extremities, 1+ patellar, 0 at ankles
Coordination/ Gait: Normal

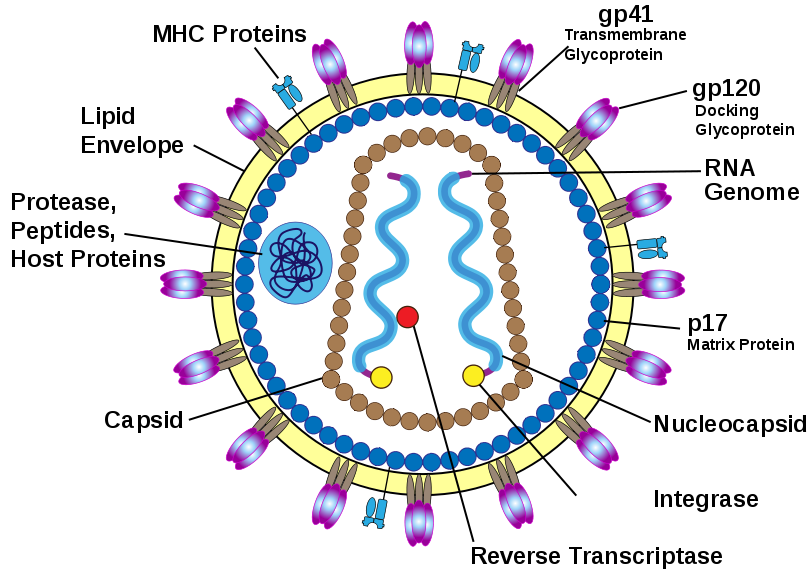
Diagnostic Tests

- CMP and CBC: normal
- Thyroid panel: normal
- Ammonia: 35
- UA: negative
- UDS: negative
- B12: 937
- Folic acid: 8.1
- RPR: negative



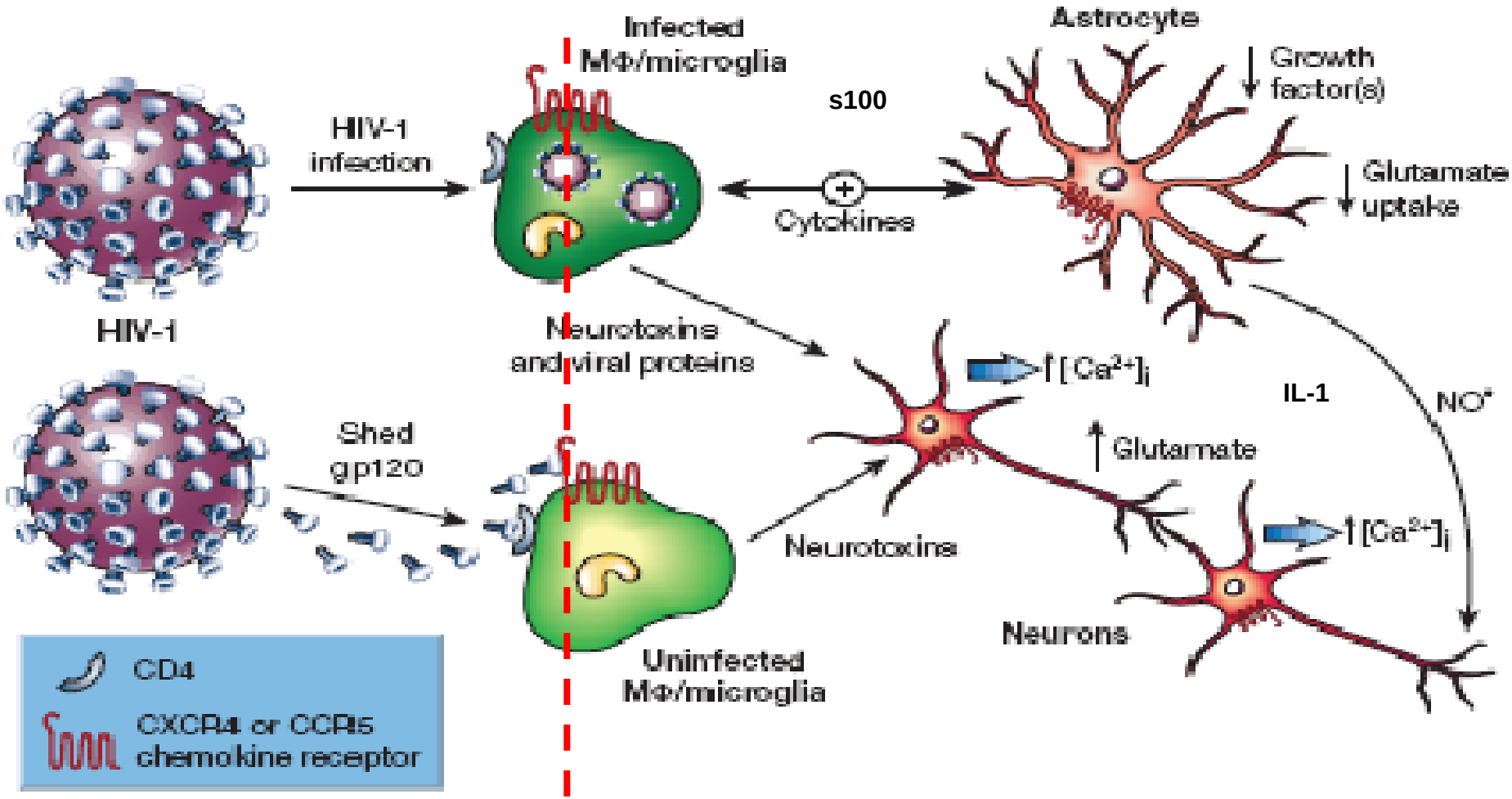
- CD4 cell count = 489 (Nadir: 54)
- Plasma HIV Viral Load= undetectable
- Neuroimaging: Unremarkable

HAND Pathophysiology and Demographics



Clifford and Ances, *Lancet Infect Dis*, 2013

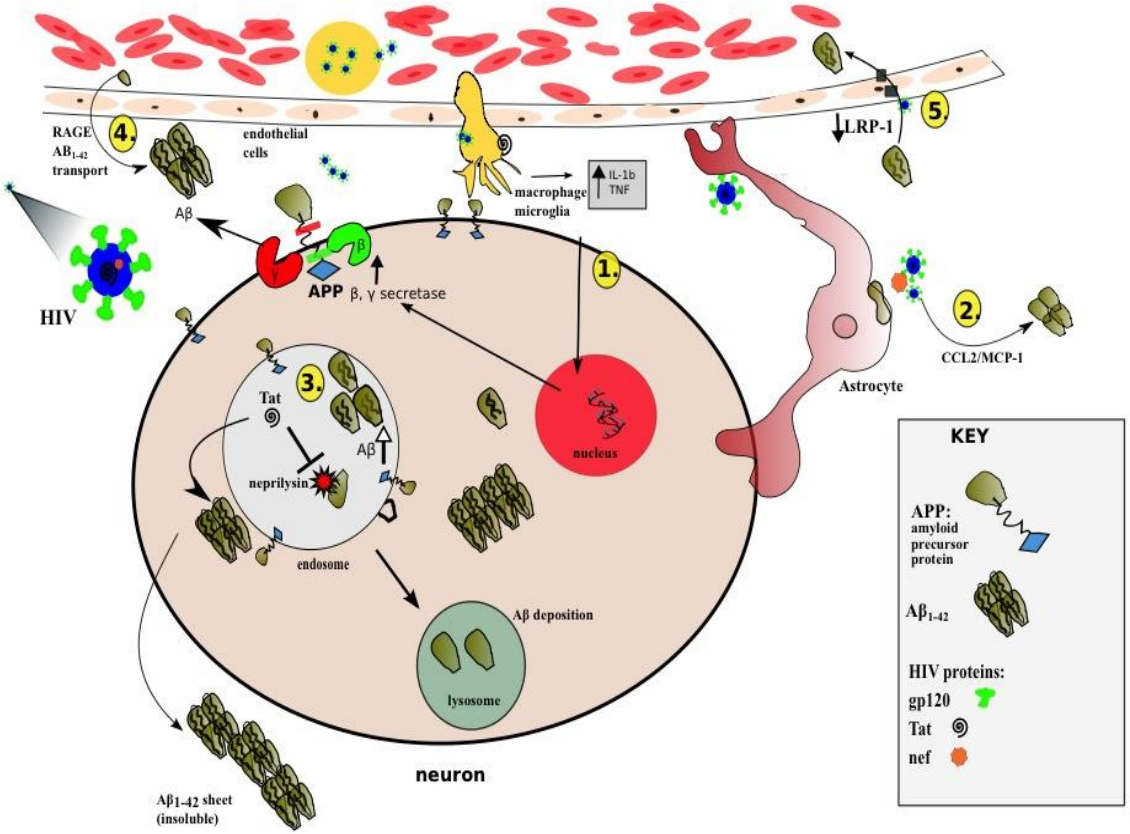
HAND Pathophysiology



Blood Brain Barrier

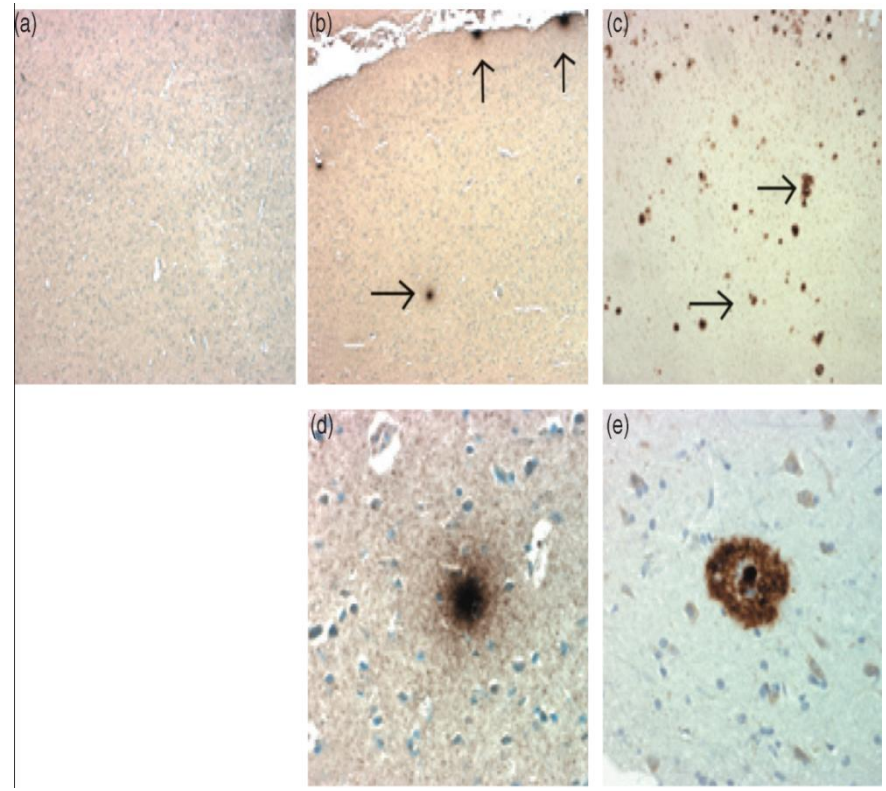
Modified from Kaul et al. *Nature*, 2001

Amyloid Metabolism in HIV



Ortega and Ances, *J Neuroimmune Pharmacol*, 2014

HIV- **HIV+** **AD**



Rempel and Pulliam, *AIDS*, 2005

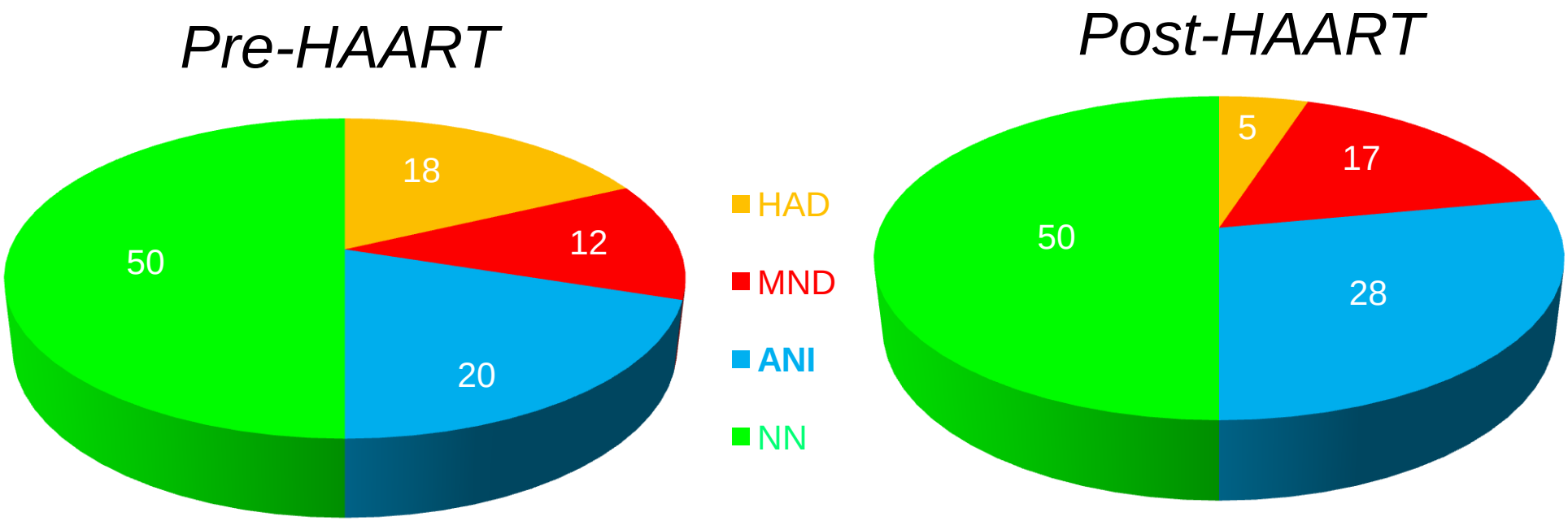
HAND Criteria in the Research Setting- Are Additional Biomarkers Needed?

	Neurologically Normal (NN)	Asymptomatic Neurocognitive Impairment (ANI)	Mild Neurocognitive Disorder(MND)	HIV Associated Dementia (HAD)
Global Deficit Score (GDS)	0	0.5	0.5	>1
Impairment in ≥ 2 Cognitive domains (> 1SD)	No	Yes	Yes	Yes (> 2 SD)
Impairment in Activities of Daily Living	No	No	**Yes- Mild**	Yes- Marked

Antinori et al., *Neurology,* 2007

- **No neuroimaging or cerebrospinal measures are included in the criteria.**

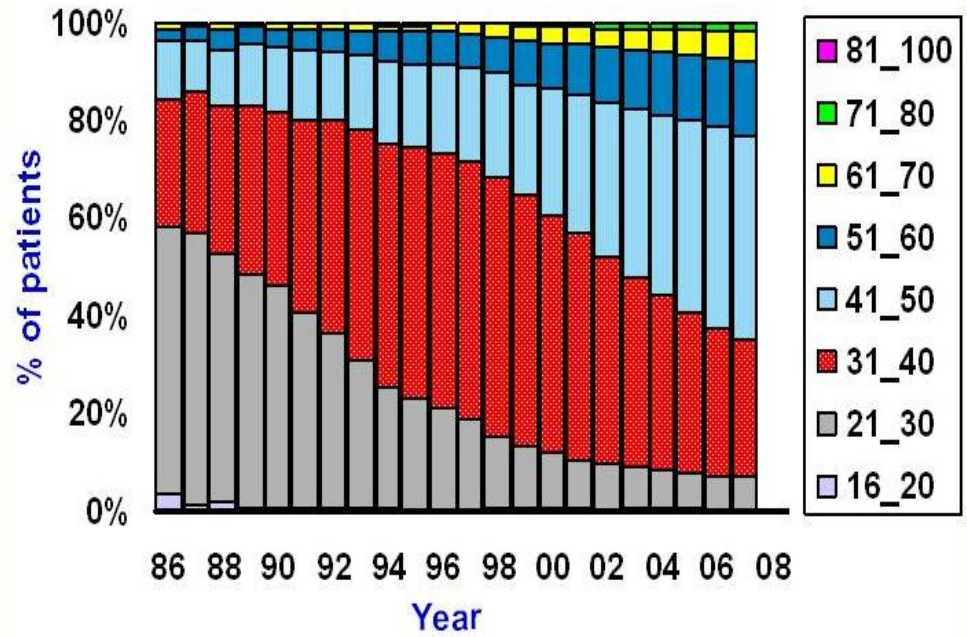
The Continuing NeuroHIV Puzzle: HAND in the Pre and Post-HAART Eras



Adapted from: Heaton, et al. *Neurology* 2010. Also: Robertson, et al. *AIDS* 2007; Simioni, et al. *AIDS* 2010; Garvey *HIV Clin Trials* 2011; Cysique & Brew, *Journal of Neurovirol* 2011; Meyer et al. *Neuroepidemiology* 2013

- **Incidence but not prevalence of HAND has declined with HAART**

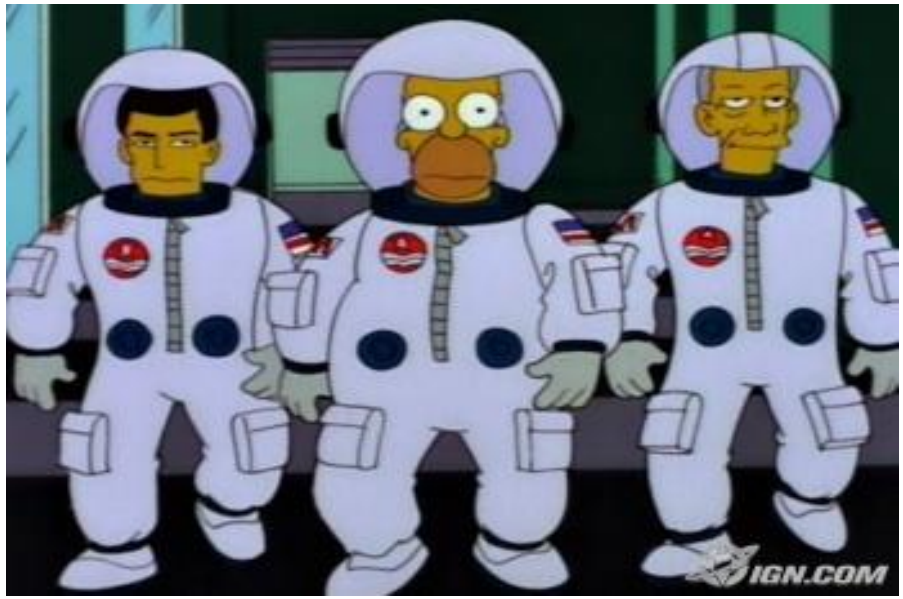
What is the Relationship Between HIV and Aging in the Brain?

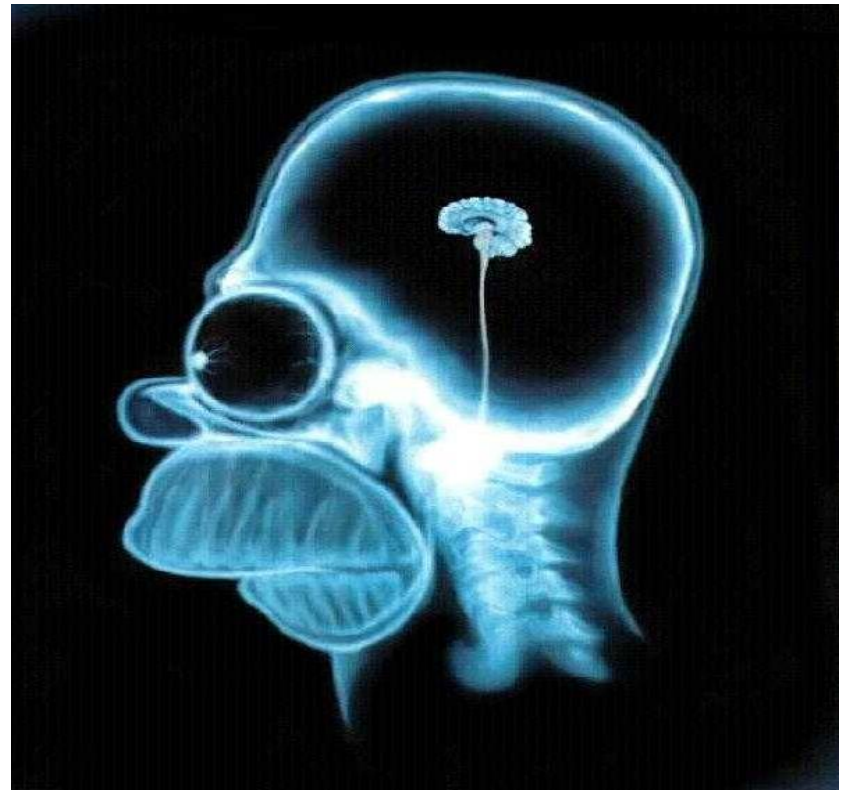


Clifford and Ances, *Lancet Infect Dis*, 2013

- **By 2015 ~ 50% of all HIV+ patients will be > 50 years old**

Effros et al. *CID*, 2008

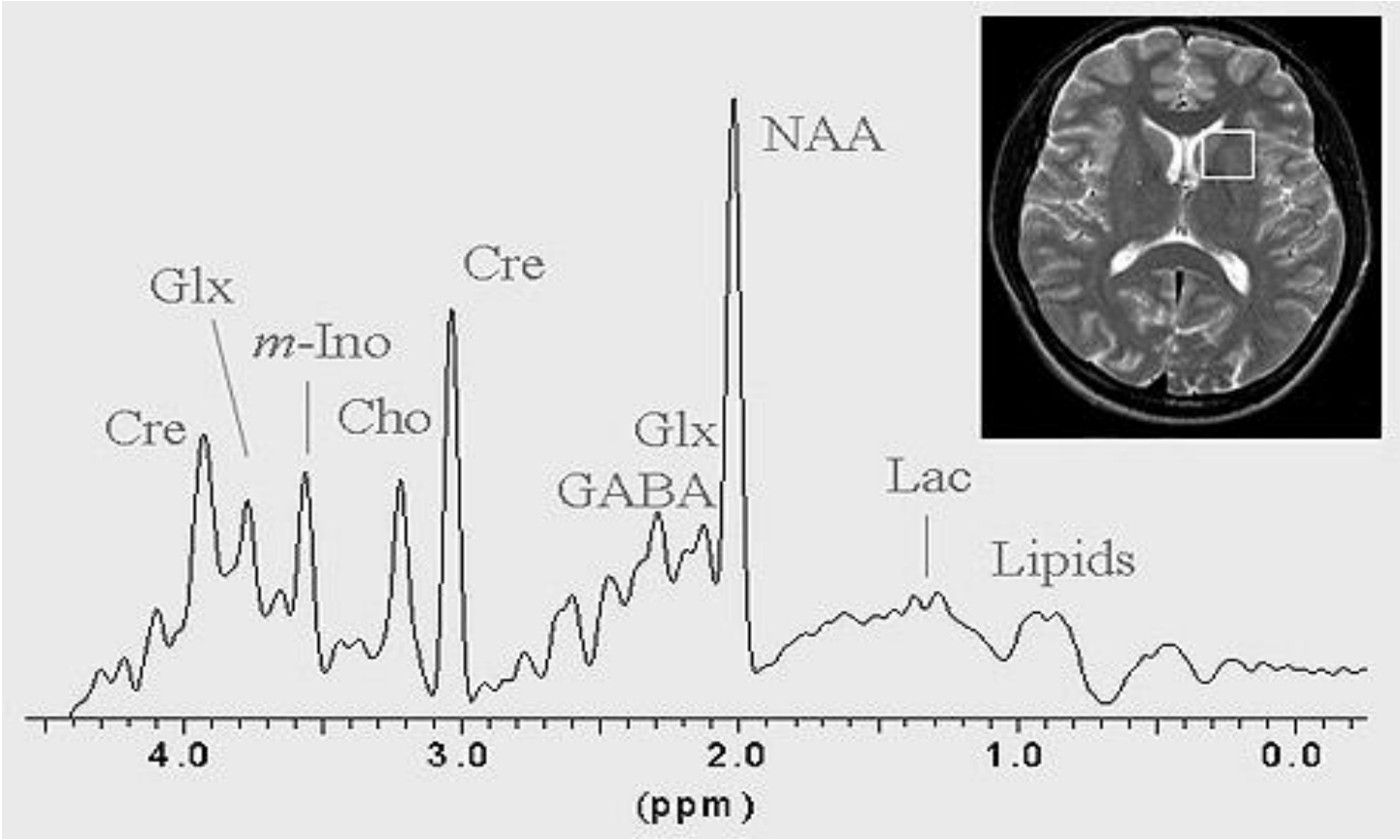




Advanced Neuroimaging Techniques

Masters and Ances, *Semin Neurol*, 2014

Magnetic Resonance Spectroscopy (MRS) Measures Brain Metabolites



NAA= N-acetyl aspartate (neuronal function)

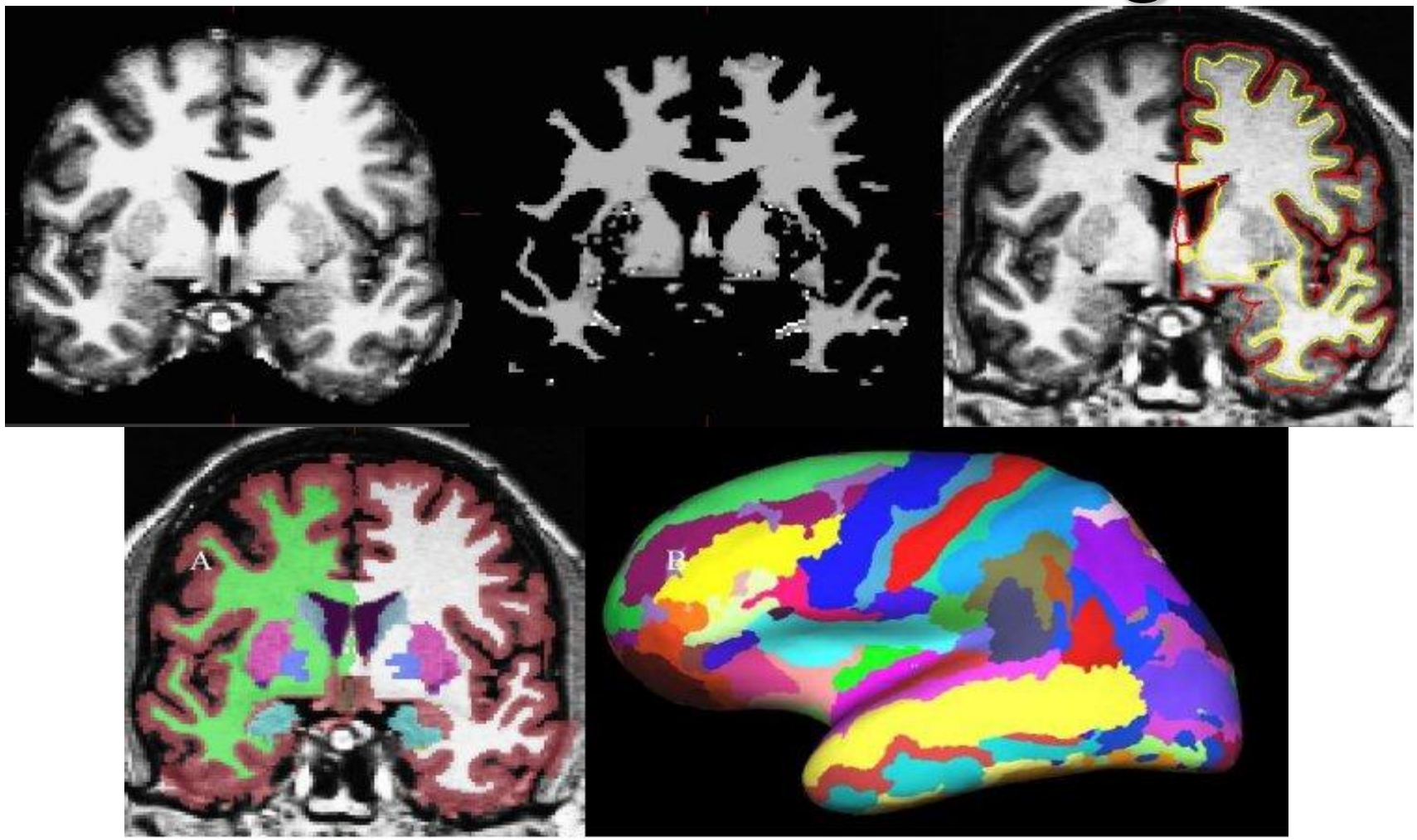
Cho= Choline (membrane turnover)

Lac= Lactate (neuroinflammation)

Cre=Creatine (reference measure)

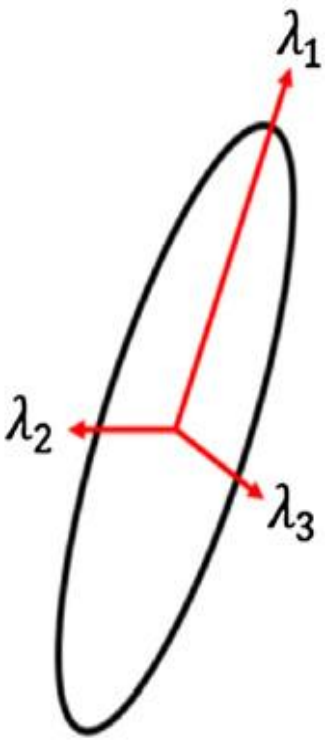
Blamire et al. *Neurology*, 2012

Volumetric Brain Segmentation is Performed on T1 Images

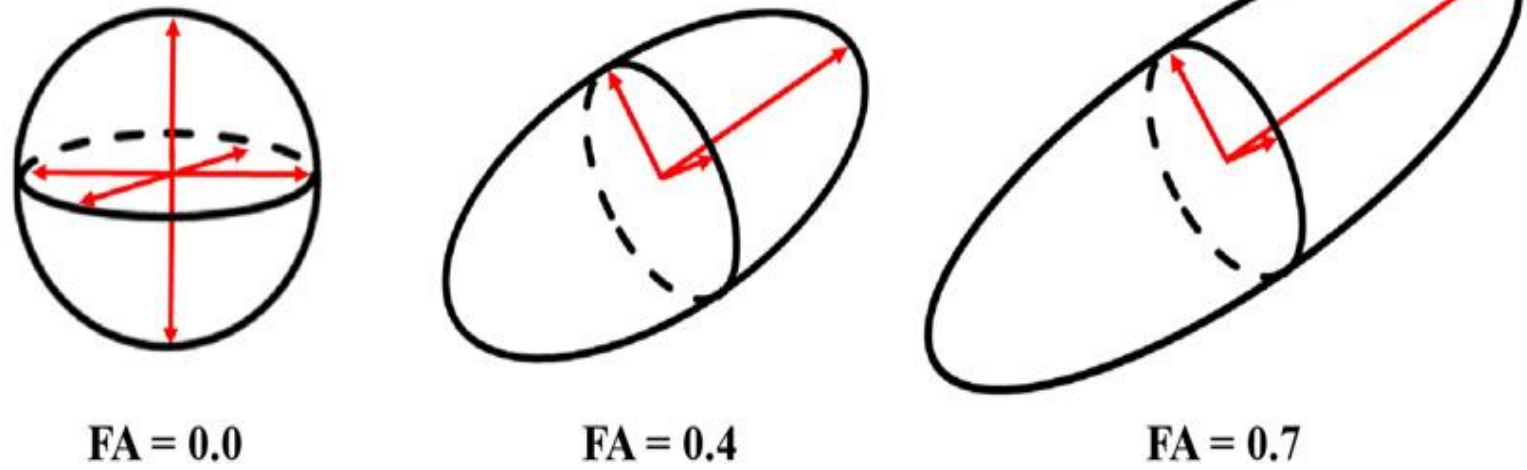


www.ftp.nmr.mgh.harvard.edu

Diffusion Tensor Imaging Measures White Matter Changes



Isotropy ***Anisotropy***



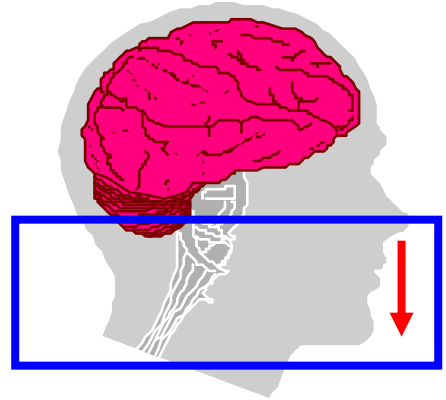
CSF and Grey Matter

White Matter

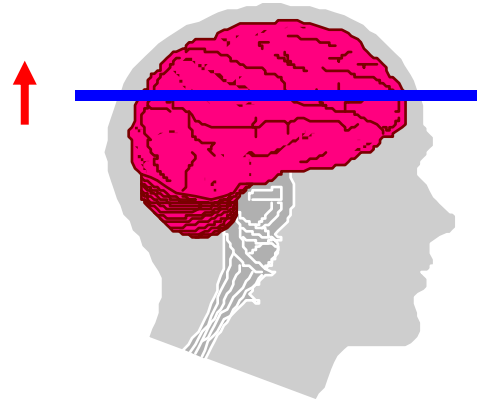
Gold et al. *Biochim Biophys Acta*. 2012

Arterial Spin Labeling (ASL) Measures Cerebral Blood Flow (CBF)

1:

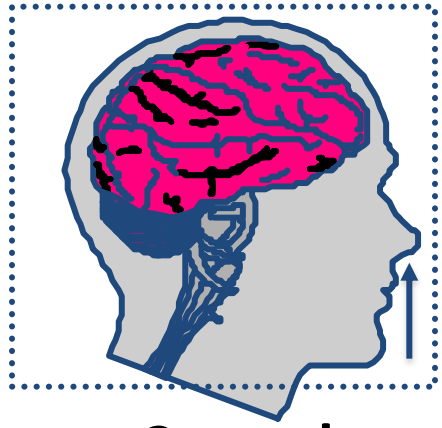


Tag by Magnetic Inversion

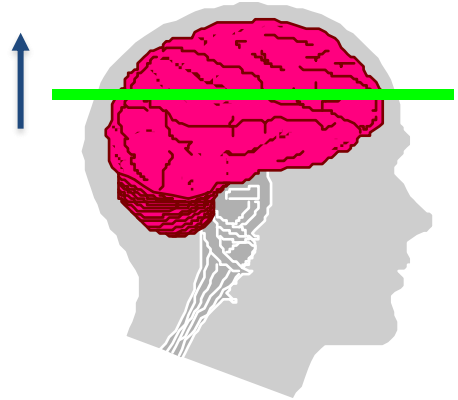


Acquire image

2:



Control



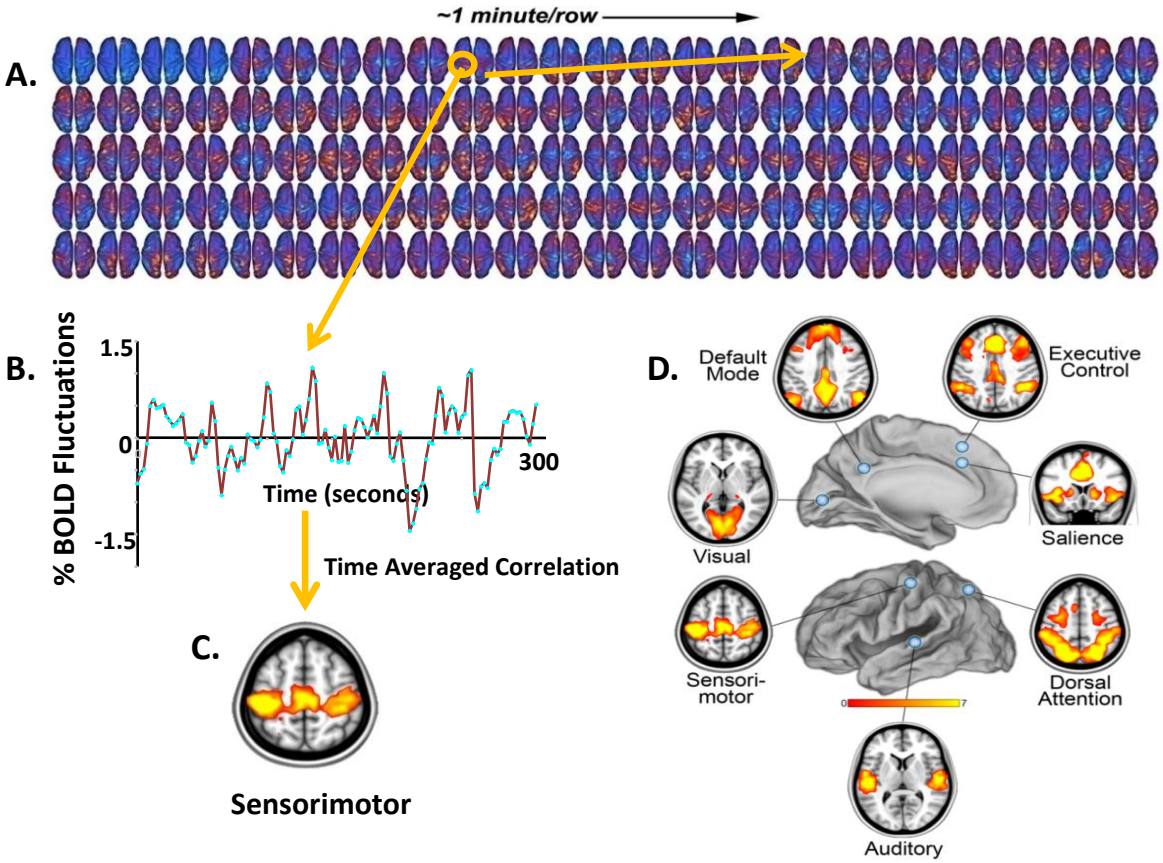
Acquire image

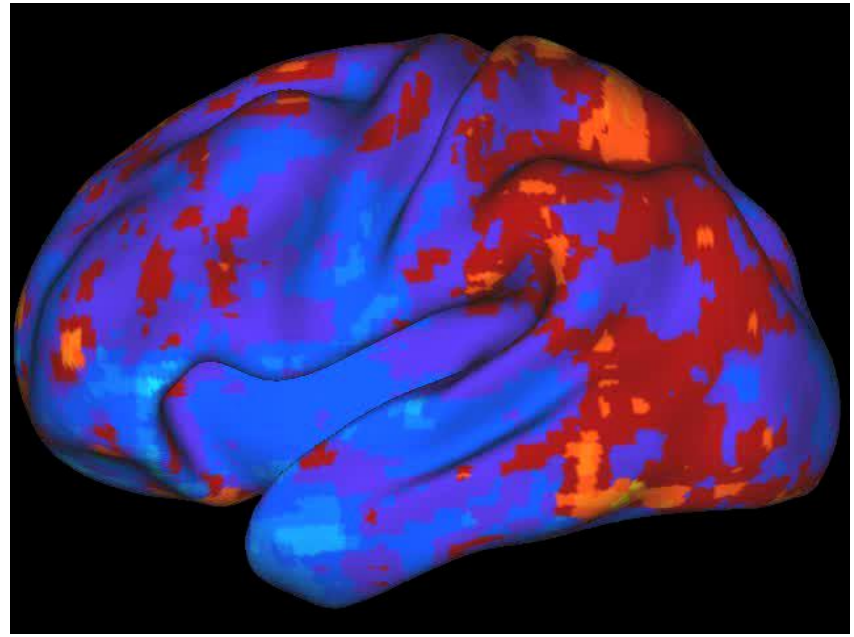
Ances et al., *Neurology*, 2006

Control - Tag ∝ CBF (mL/100mL/min)

Resting State Functional Connectivity in Clinical Practice?

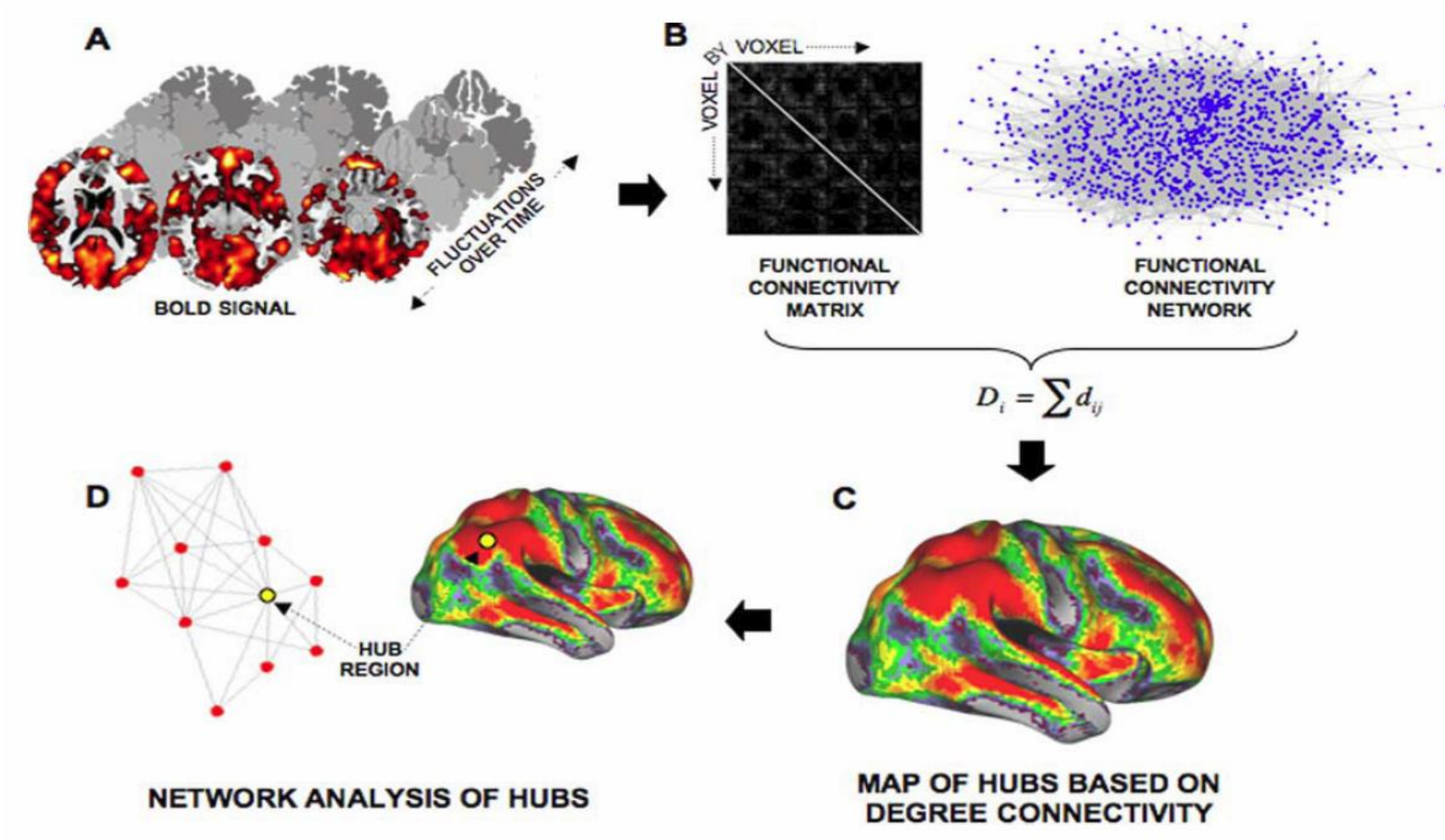
Resting State Functional Connectivity Magnetic Resonance Imaging (rs-fcMRI) Measures Brain Correlations





Raichle, *Brain Connectivity*, 2011

Graph Models of rs-fcMRI: The Next Level



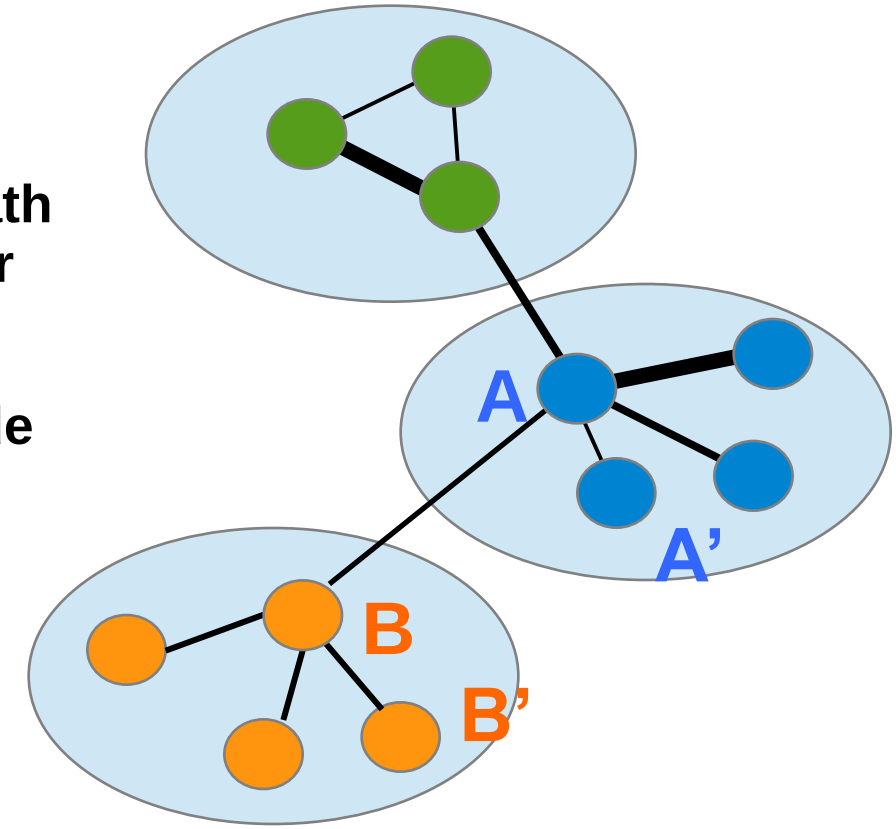
Buckner et al. *J.Neurosci*, 2009

Graph Theory 202

Hubness (Node importance)

Closeness: average weighted shortest path length between a given node and all other nodes (A,B)

Eigenvector centrality: centrality of a node depends on the centrality of that node's neighbor (A',B')

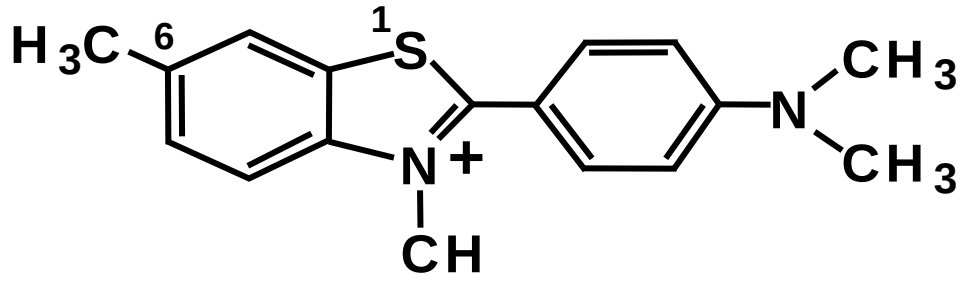


Entropy (Disorder)

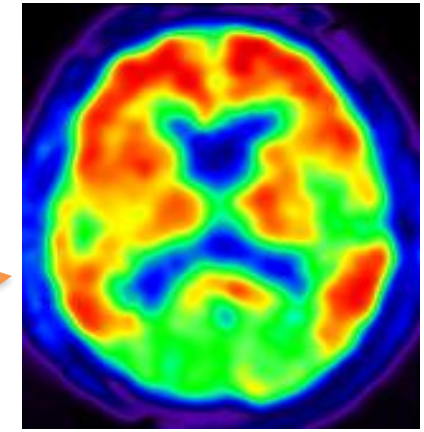
Diversity: measure of graph entropy (variability in connections at a given node) (A,B)

- Measures can be applied at the global, network, and node levels

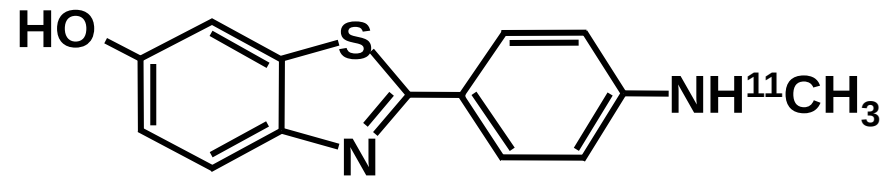
Pittsburgh Compound B (PiB) Imaging Measures Amyloid Deposition



Histology - Thioflavin T



PET Imaging -
[^{11}C]6-OH-BTA-1 (PIB)



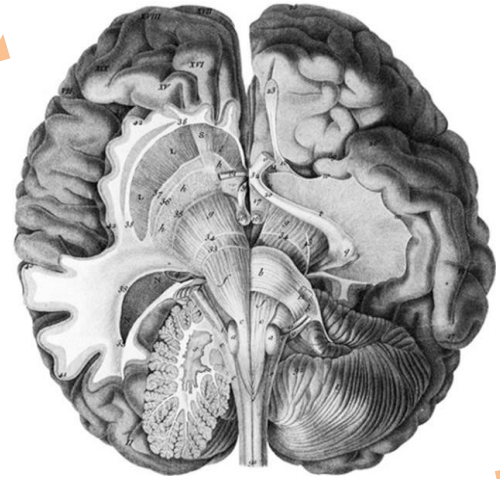
Klunk et al, *Ann Neurol,* 2004

Neuroimaging Results

Mechanisms of HIV-Related CNS Injury in the Setting of cART in Our Patient

Early impact of HIV in the CNS soon after seroconversion or "burnt out" state

Co-morbidities (substance abuse, co-infections, mood disorders)



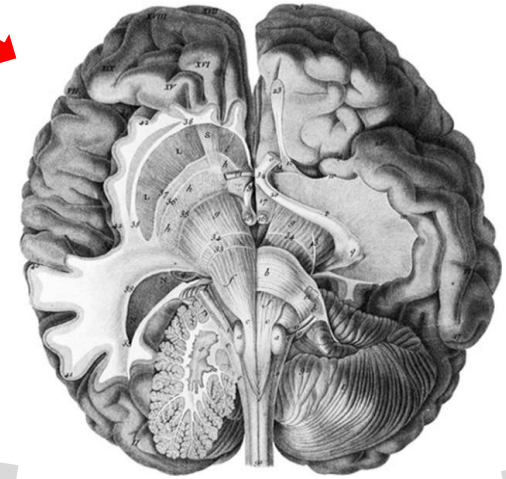
Aging

Ongoing CNS immune activation and active virus

Delayed HAART exposure or toxicity due to cART within CNS

Mechanisms of HIV-Related CNS Injury in the Setting of cART in Our Patient

Early impact of HIV in the CNS soon after seroconversion
(diagnosed in 1988)



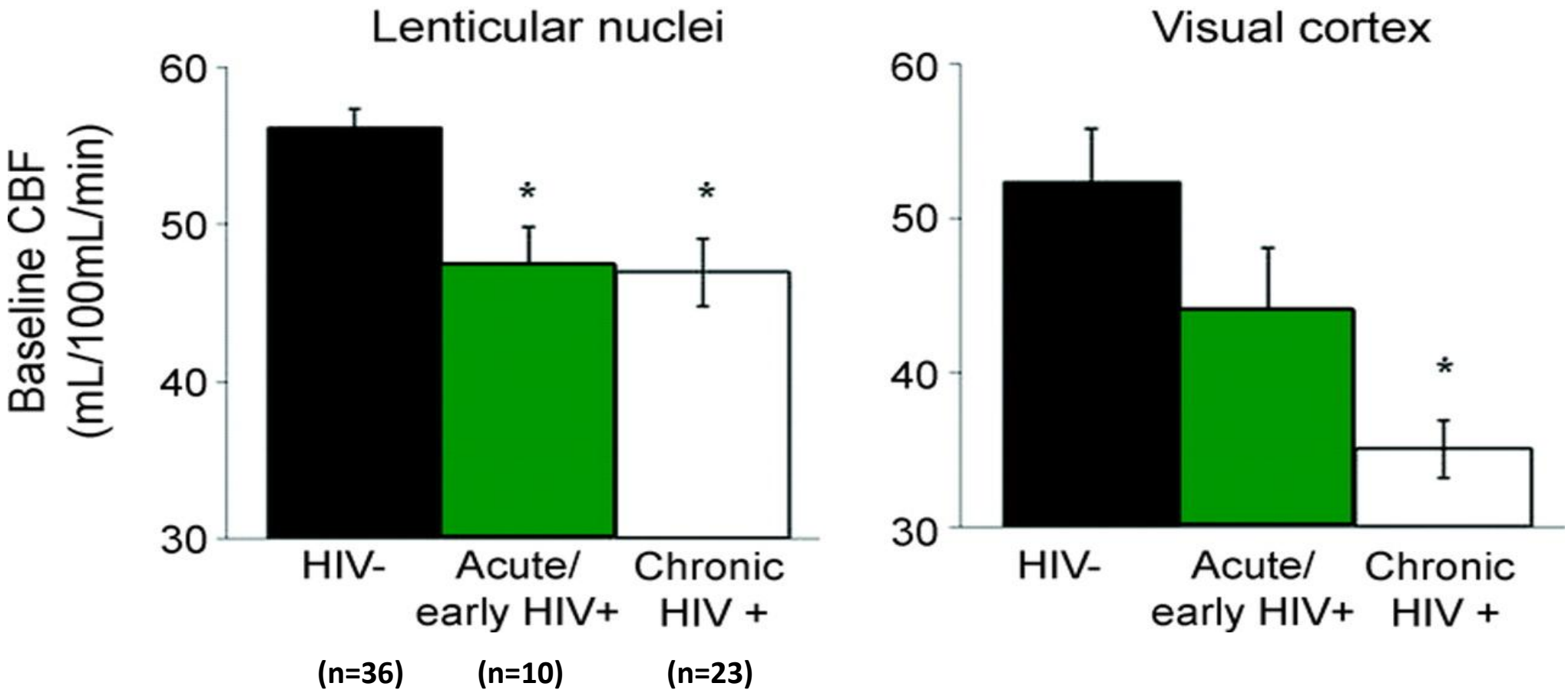
Co-morbidities (substance abuse, co-infections, mood disorders)

Aging

Delayed HAART exposure or toxicity due to cART within CNS

Ongoing CNS immune activation

Acute and Early HIV Infection Reduces CBF

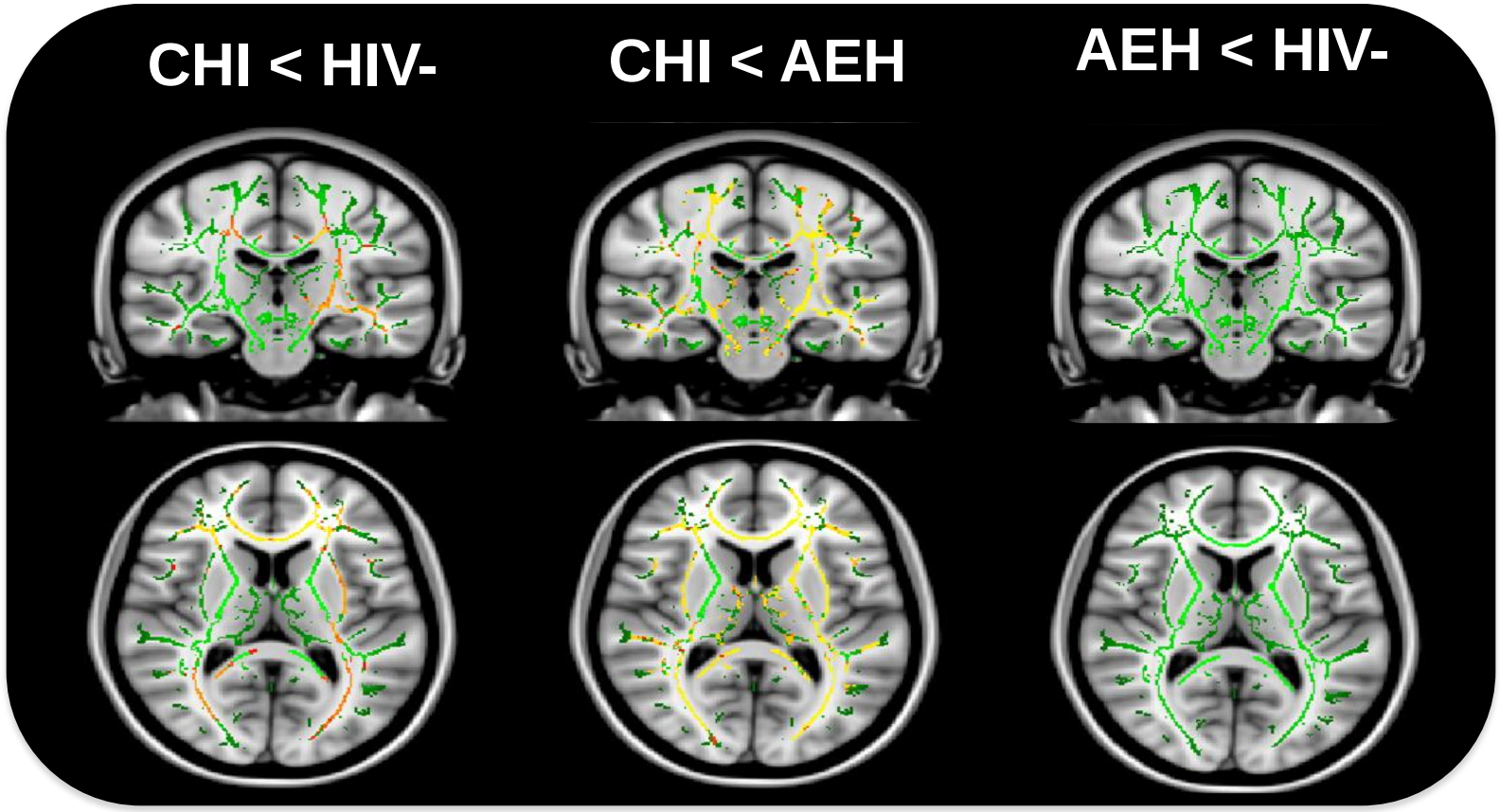


Ances et al., *Neurology,* 2009

Acute and Early HIV Infection Damages the White Matter

Fractional Anisotropy (FA)

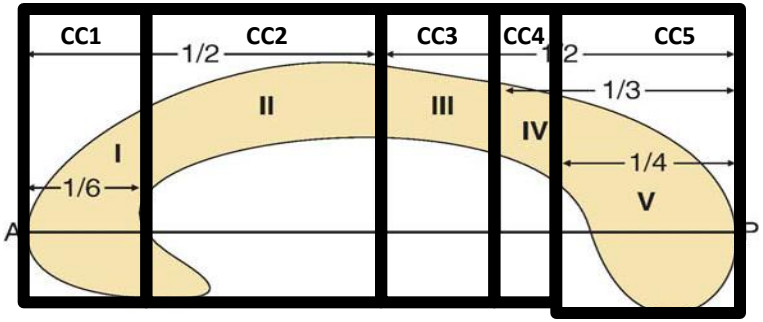
19 HIV-
62 AEH
16 CHI



Wright et al.,
under review

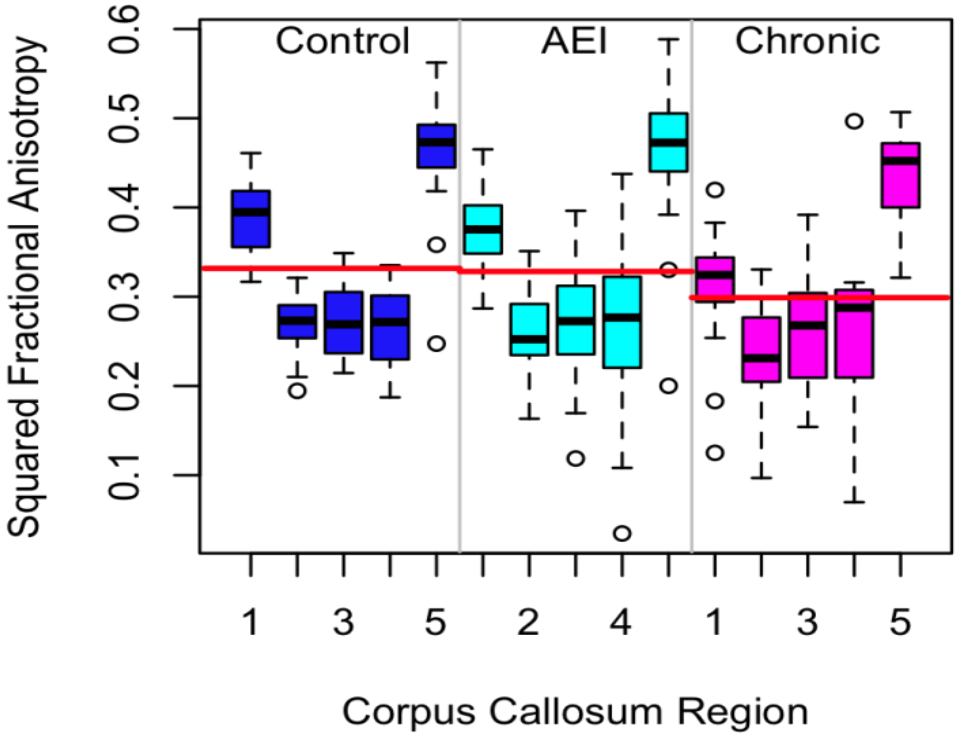
- **Plasma neopterin, CSF and plasma VL, and CD4+ cell counts correlated with FA in CHI but not AEH.**

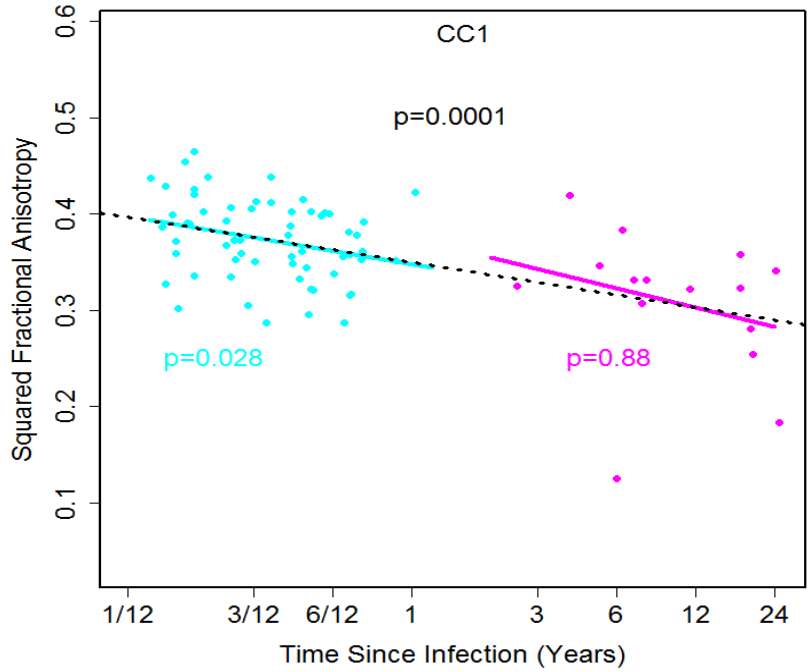
Duration of HIV Infection Affects the Corpus Callosum White Matter Integrity



19 HIV- Controls
62 AEH
16 CHI

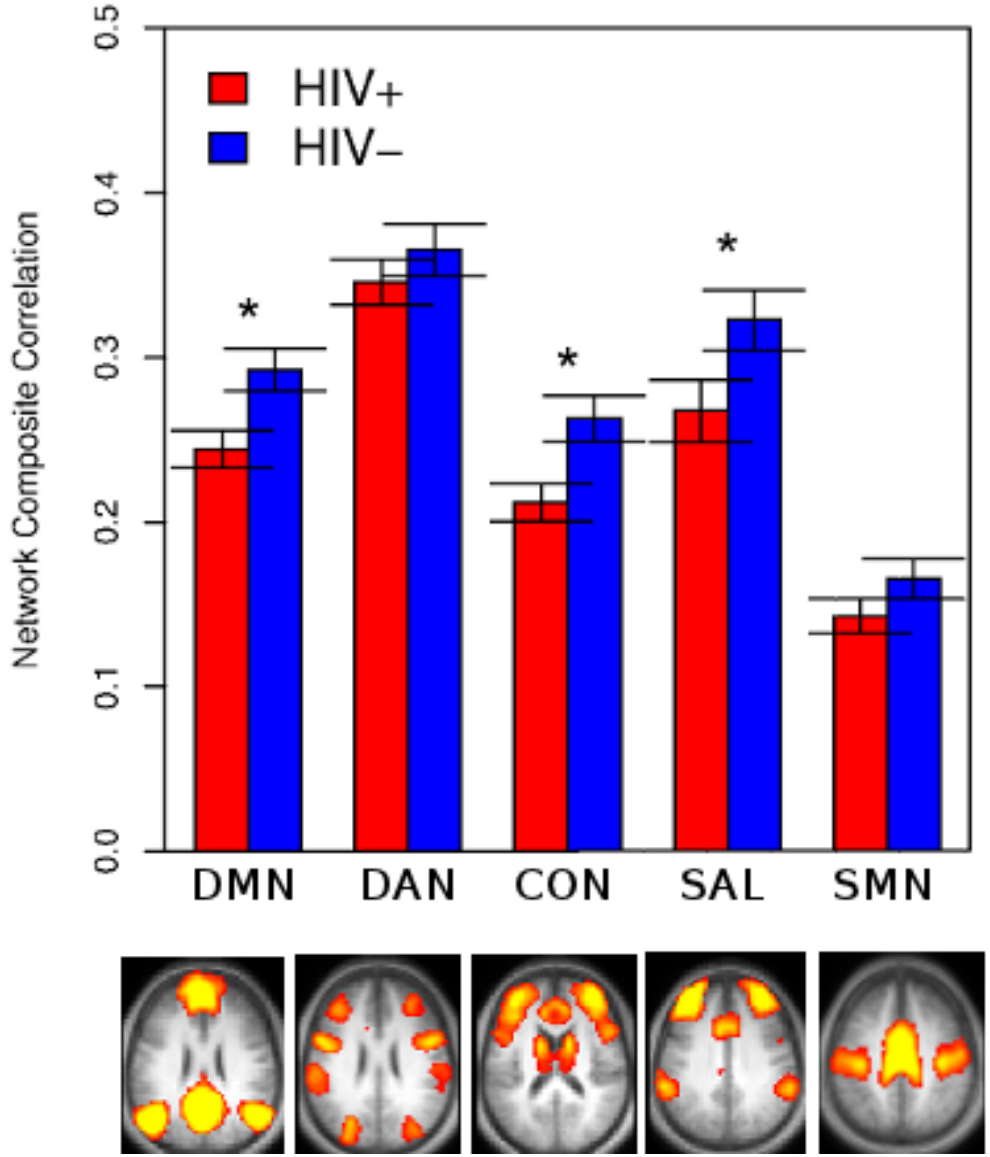
All HIV+ are untreated





Wright et al., *under review*

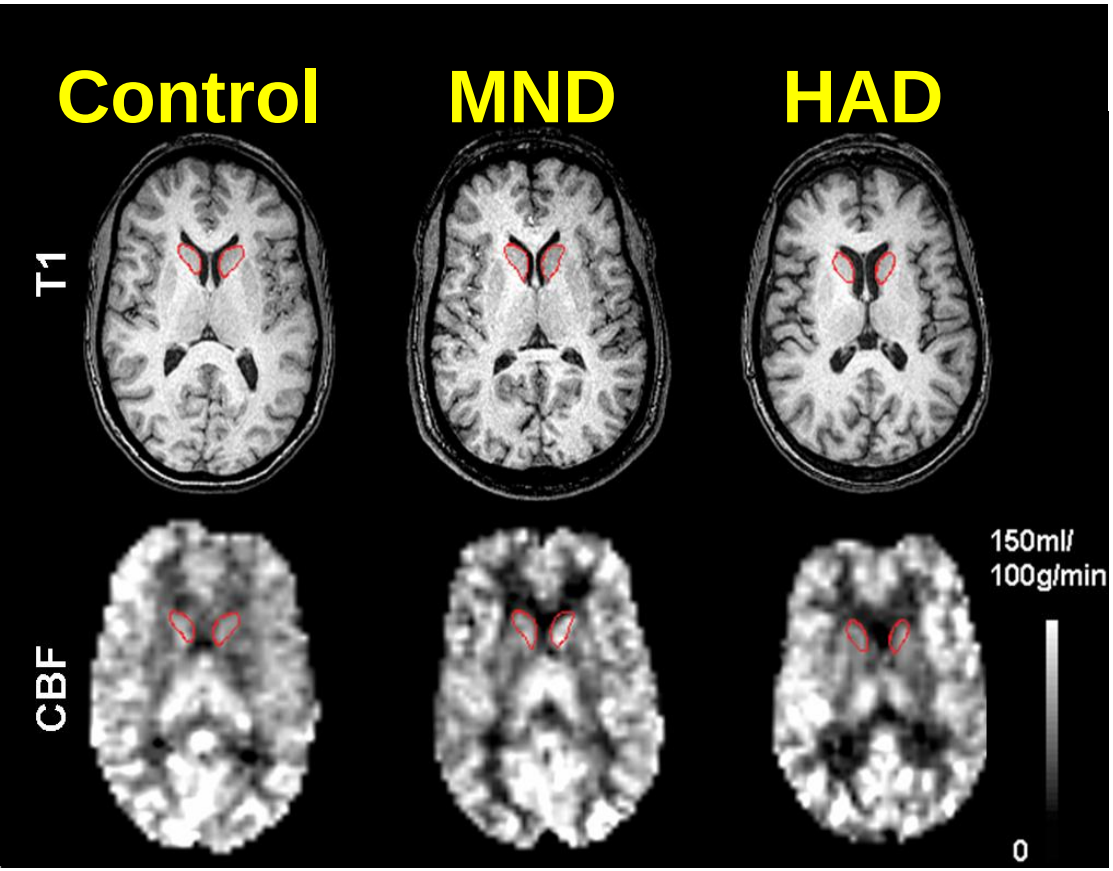
rs-fcMRI is Diminished in Chronic HIV+ Individuals

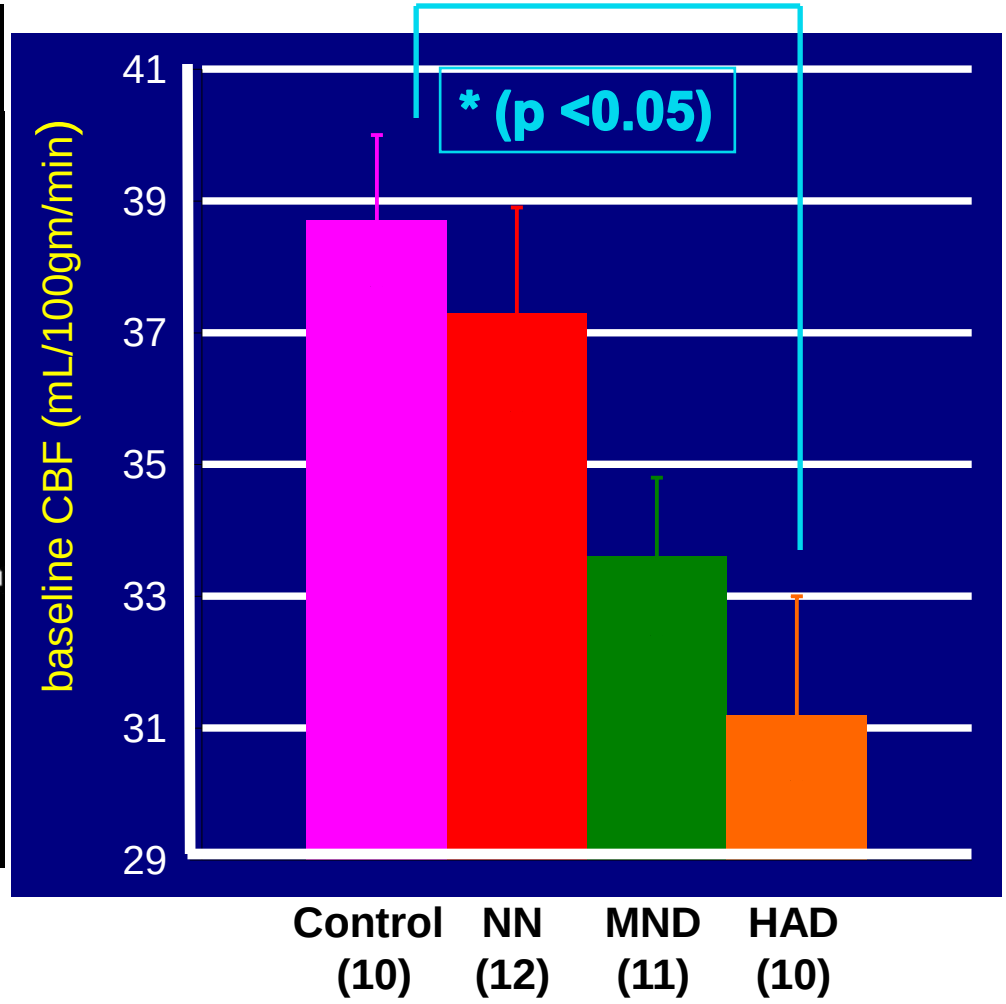


HIV+ = 58
HIV- = 53

Thomas et al., *Neurology,* 2013

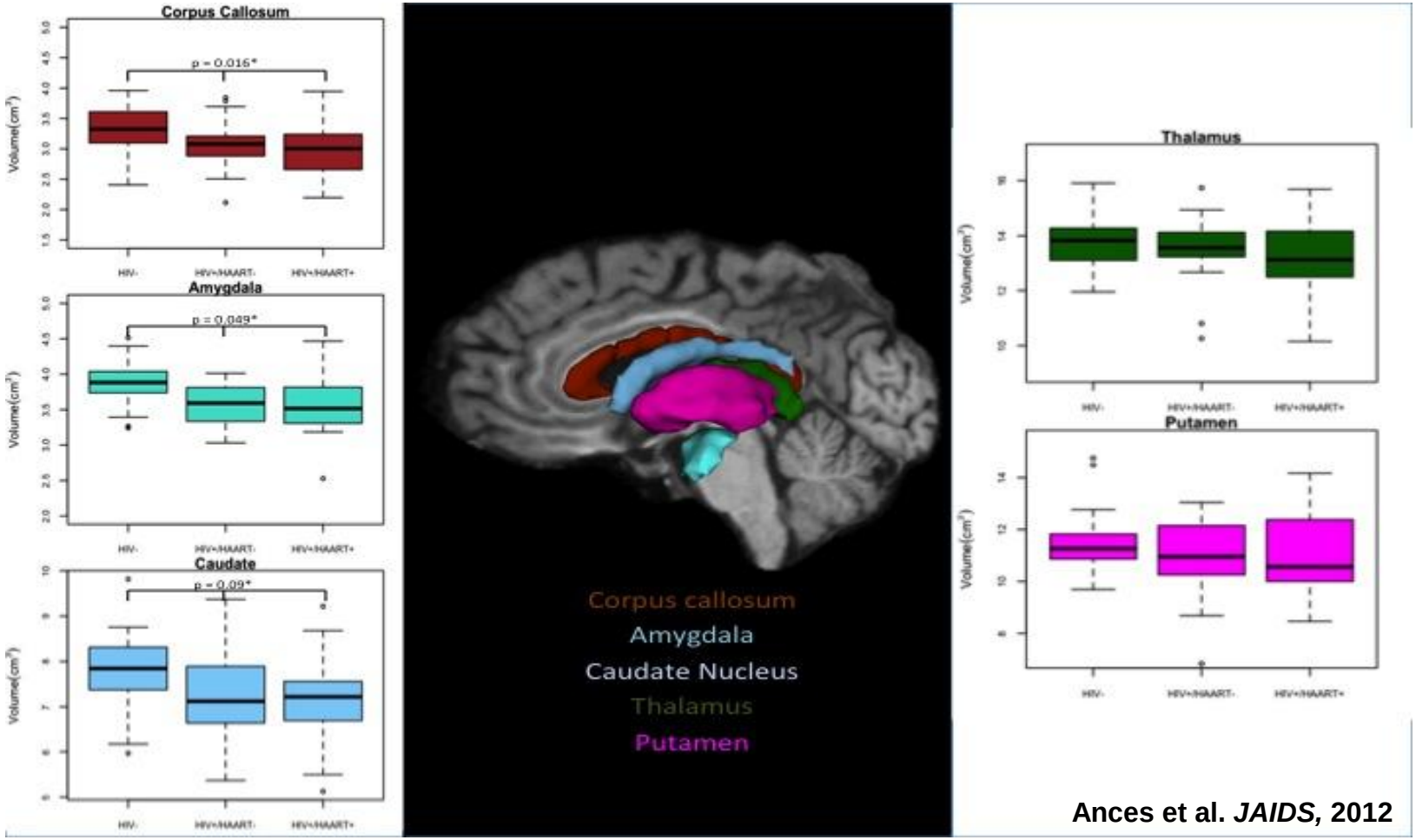
HAND Reduces Caudate CBF in Chronic HIV+ Individuals





Ances et al., *Neurology*, 2006

Brain Volumetrics Are Diminished in Chronic HIV+ Individuals



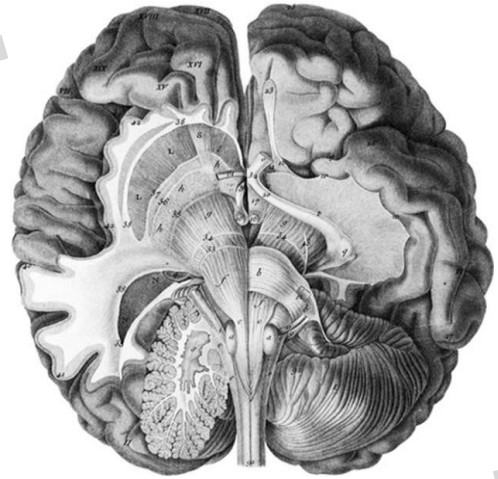
Ances et al. *JAIDS*, 2012

HIV- = 26, HIV+/HAART- = 26, HIV+/HAART+ = 26

Mechanisms of HIV-Related CNS Injury in the Setting of cART in Our Patient

Early impact of HIV in the CNS soon after seroconversion or "burnt out" state

Co-morbidities (substance abuse, co-infections, mood disorders)



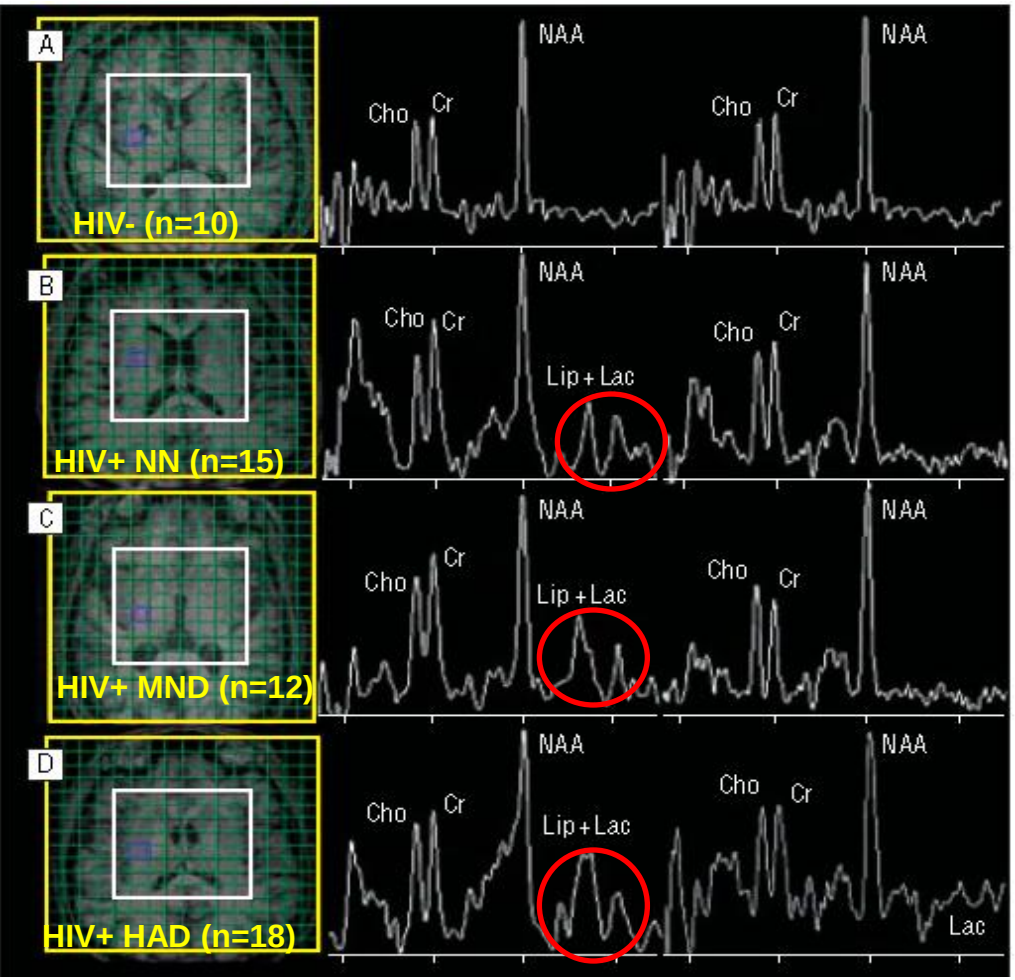
Aging

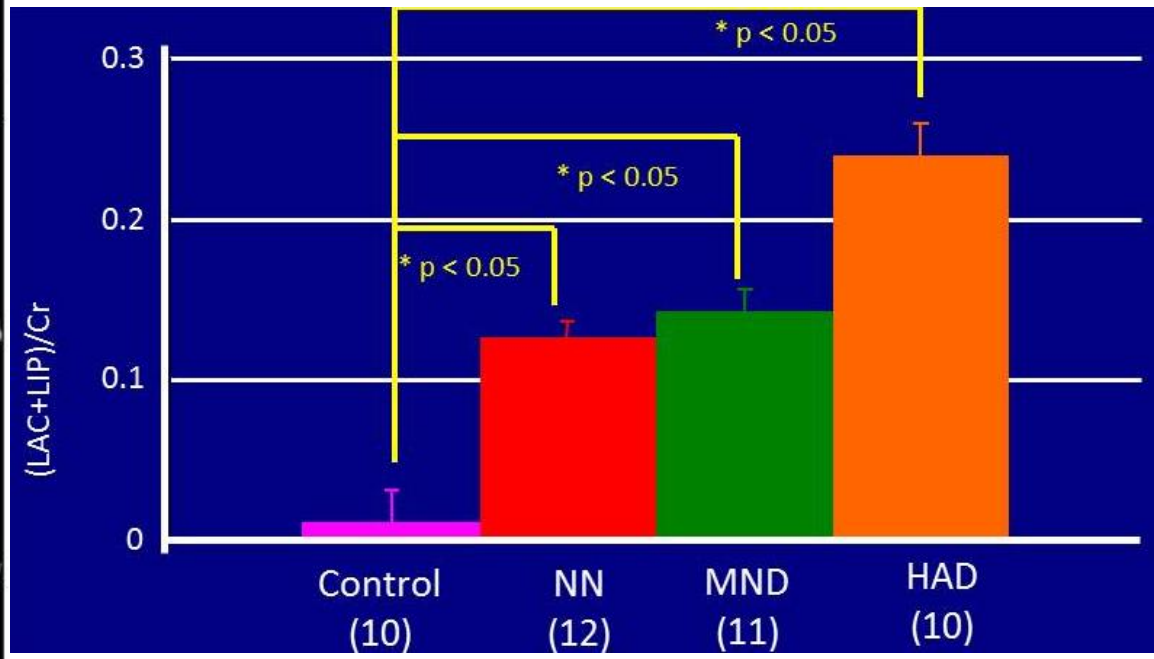
Delayed HAART exposure or toxicity due to cART within CNS

Ongoing CNS immune activation and active virus

(virologically suppressed)

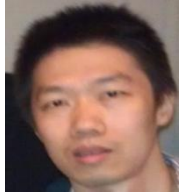
Neuroinflammation is Present in Chronic HIV+ Patients Using MRS

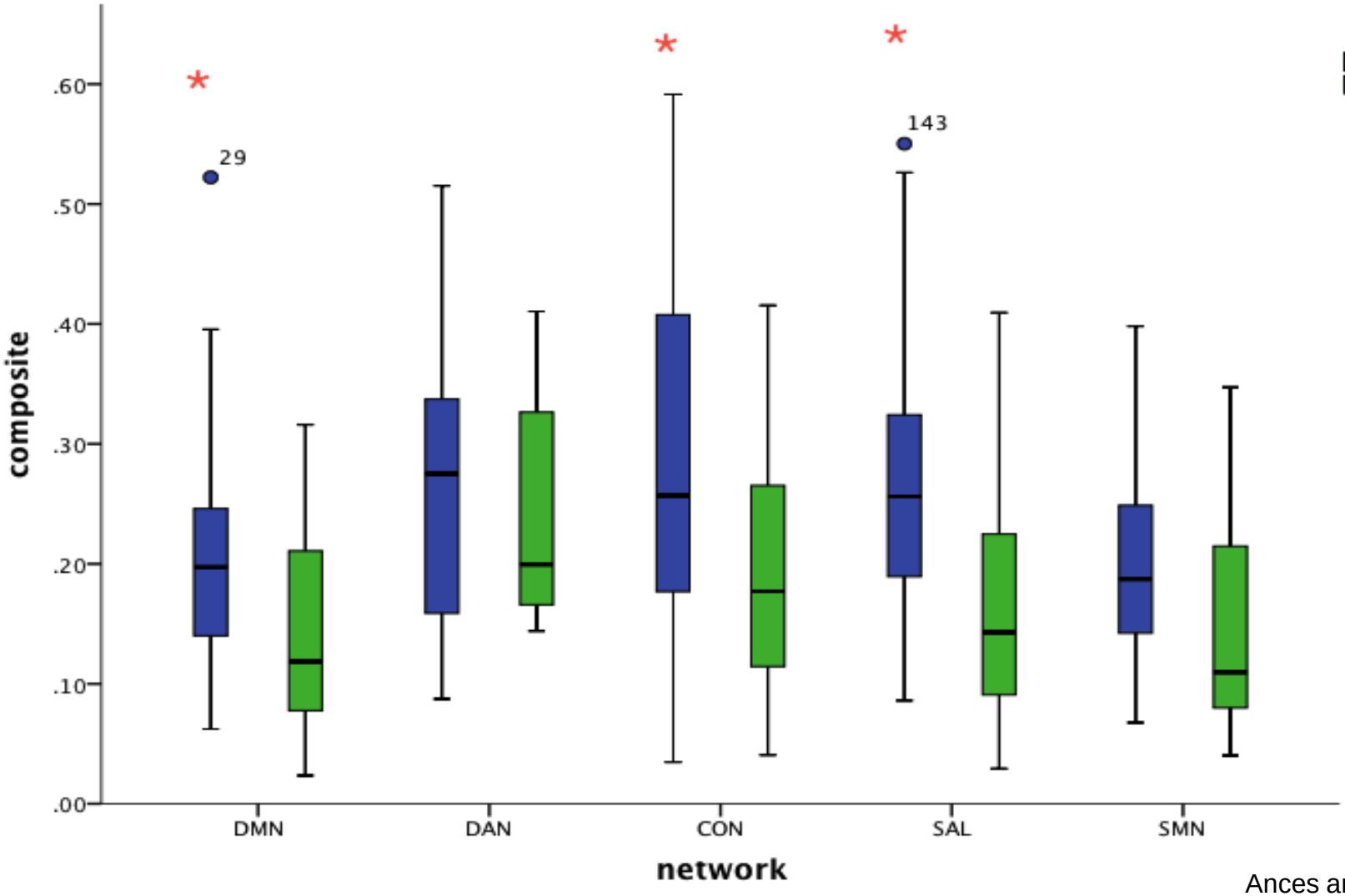




Ances et al., Archives of *Neurology,* 2007

Virologically Suppressed Older HIV+ Patients (> 60 years old) Have Greater Functional Correlations Using Rs-fcMRI





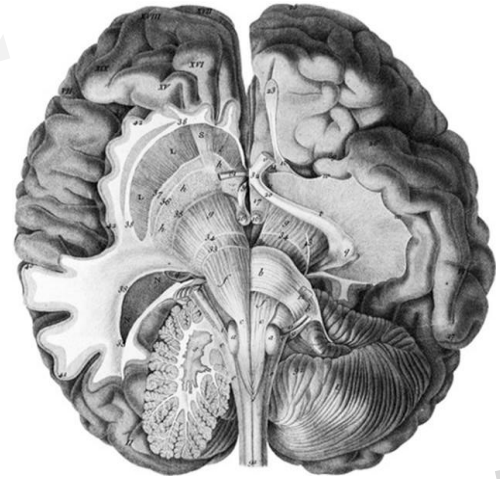
Ances and Valcour under preparation

Mechanisms of HIV-Related CNS Injury in the Setting of cART in Our Patient

Early impact of HIV in the CNS soon after seroconversion or "burnt out" state

Co-morbidities (substance abuse, co-infections, mood disorders)

(Clade B, Hepatitis C (1992), and drug abuse (1980's), and male)

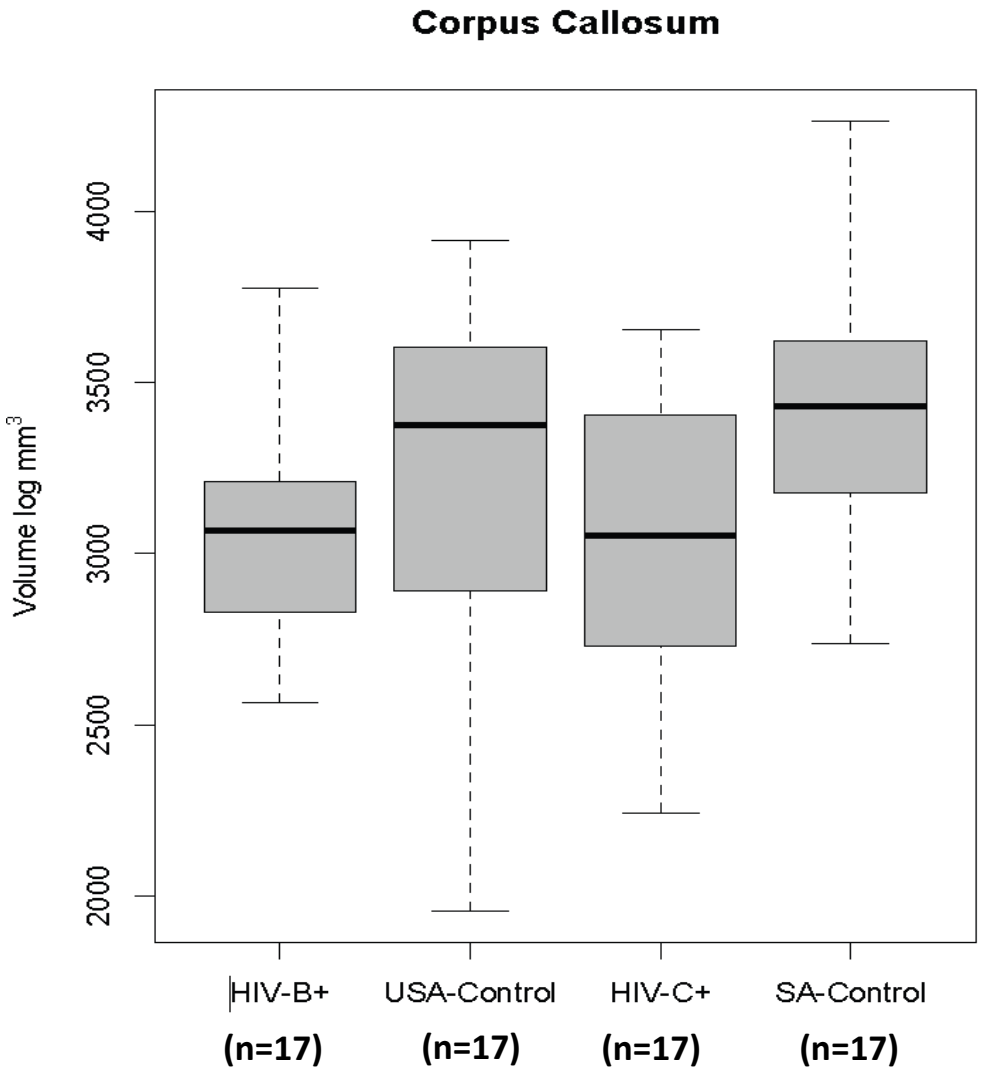


Aging

Delayed HAART exposure or toxicity due to cART within CNS

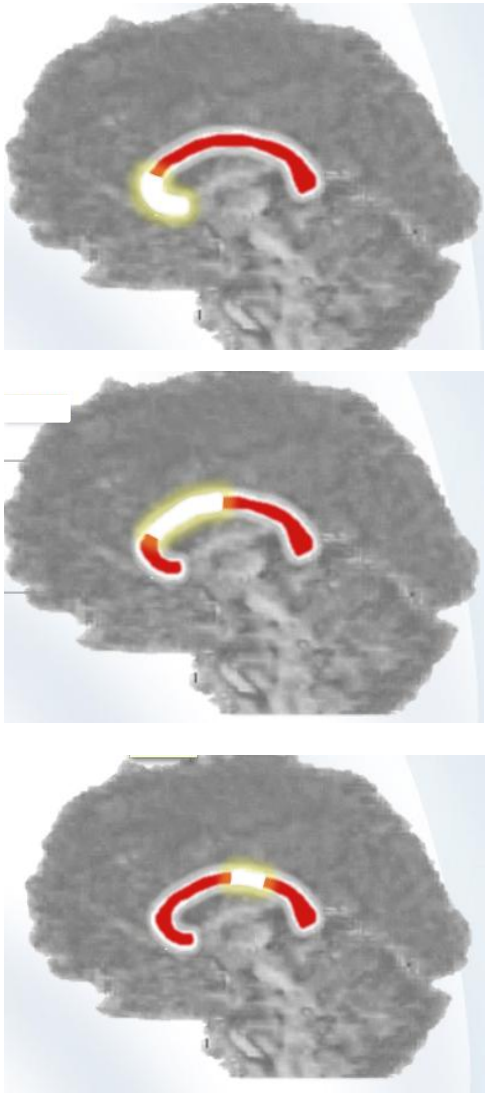
Ongoing CNS immune activation and active virus

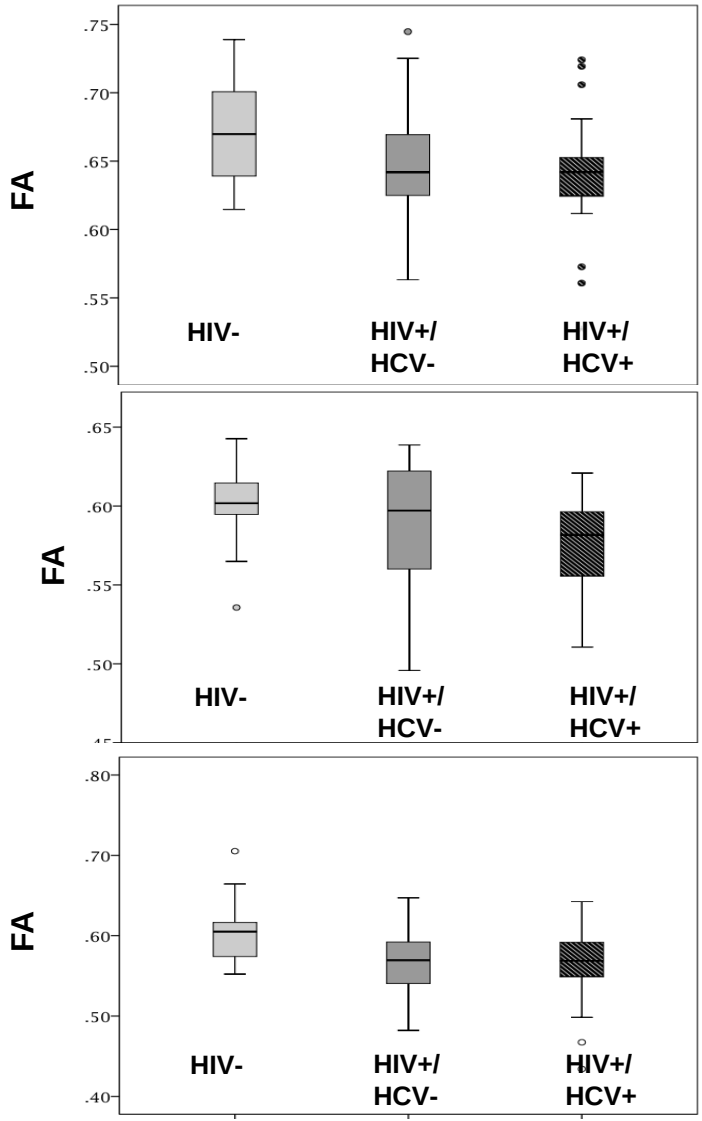
HIV Clade Subtype Does Not Affect Brain Volumetrics



Ortega et al., *J Neurovirol.*, 2013

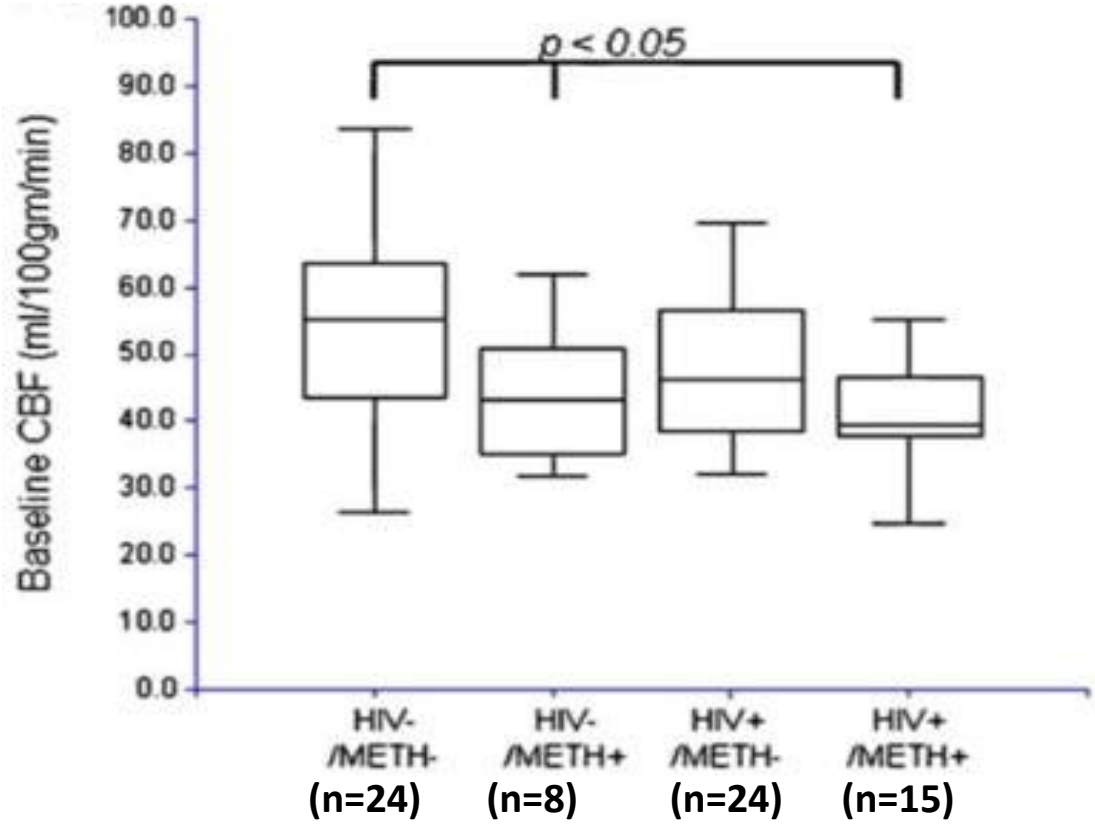
No Additive Effect of Hepatitis C (HCV) Co-infection on DTI Metrics





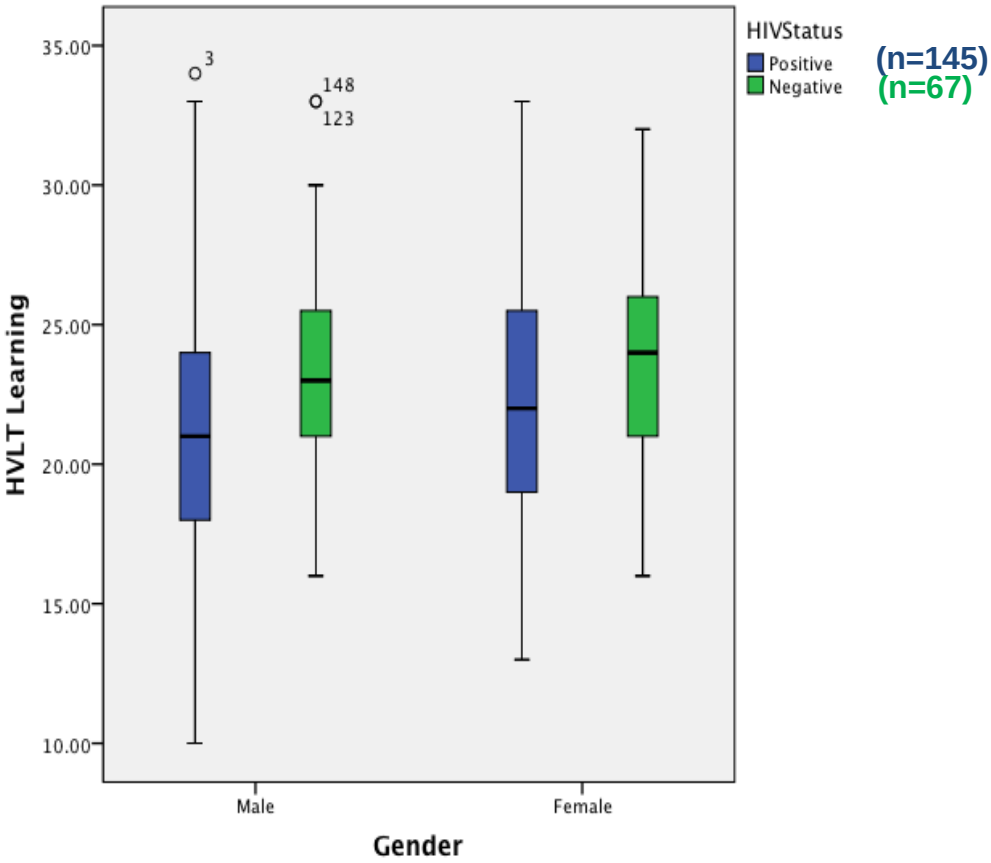
Heaps et al., *under review*

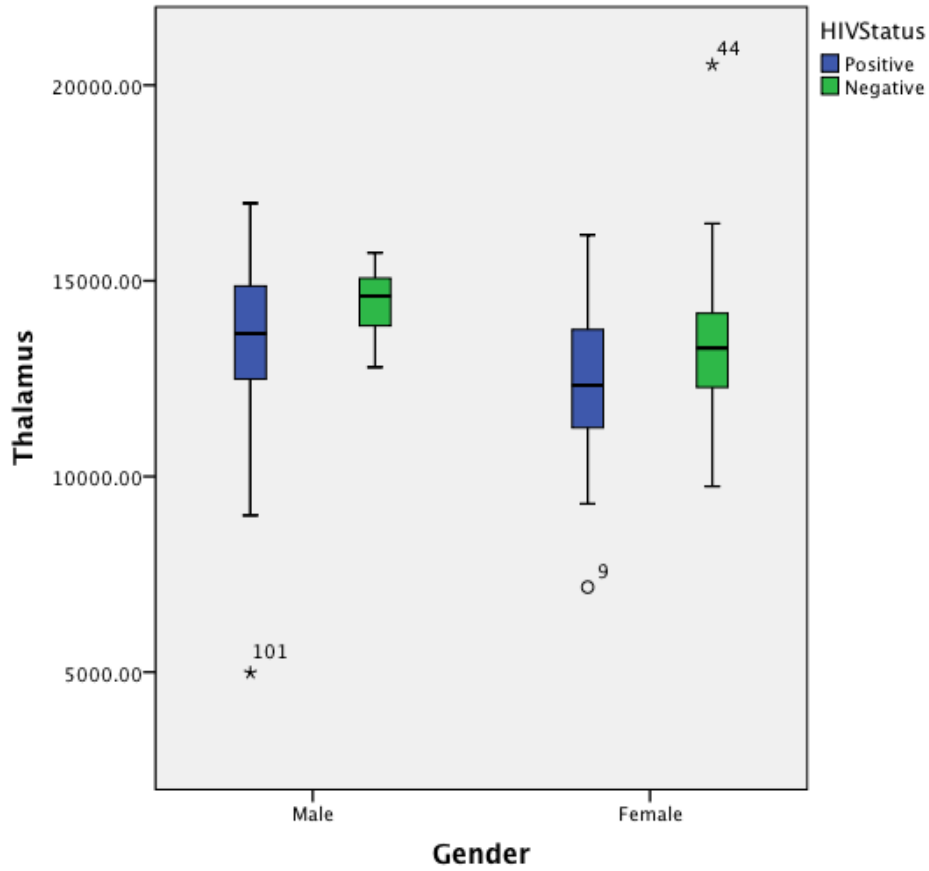
HIV and Previous Methamphetamine Use Independently Reduce CBF



Ances et al., *J Neuroimmune Pharmacol.,* 2011

HIV Status and Not Gender Affects Neuropsychological Performance and Neuroimaging Measures





Baker et al., under preparation

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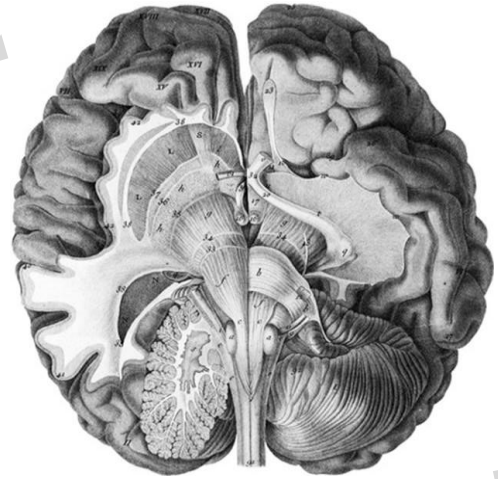
Early impact of HIV in the CNS soon after seroconversion or "burnt out" state

Co-morbidities (substance abuse, co-infections, mood disorders)



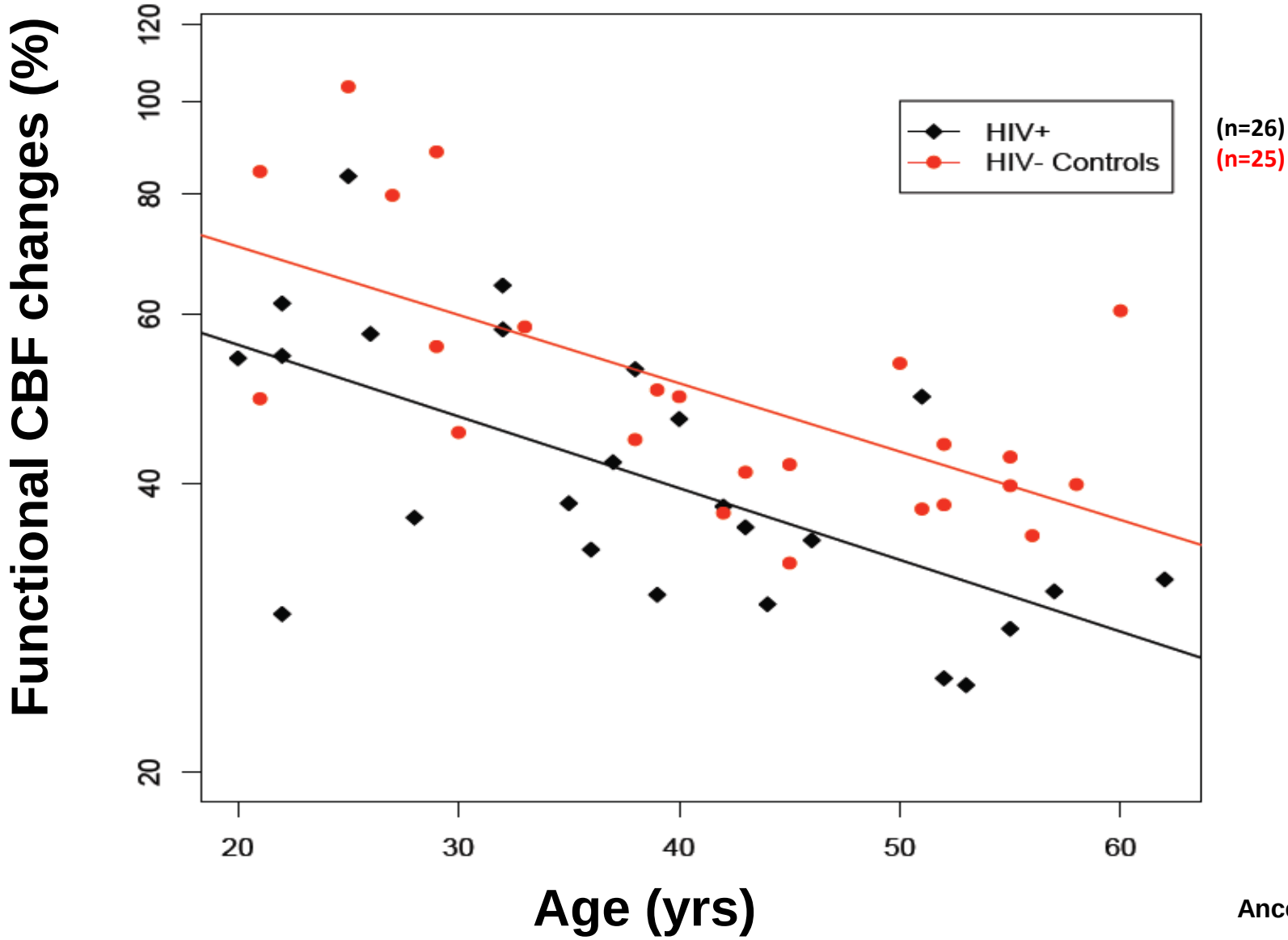
Aging

(64 years old)

Ongoing CNS immune activation and active virus

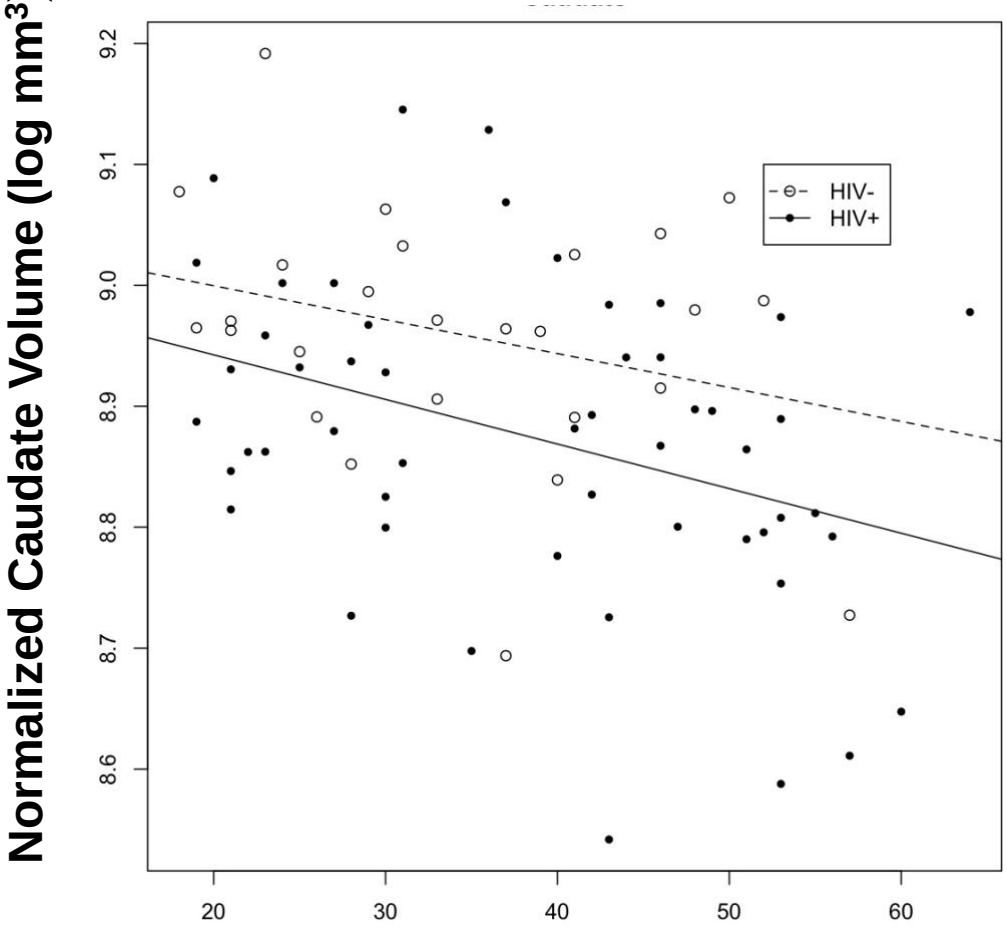
Delayed cART exposure or toxicity due to HAART within CNS

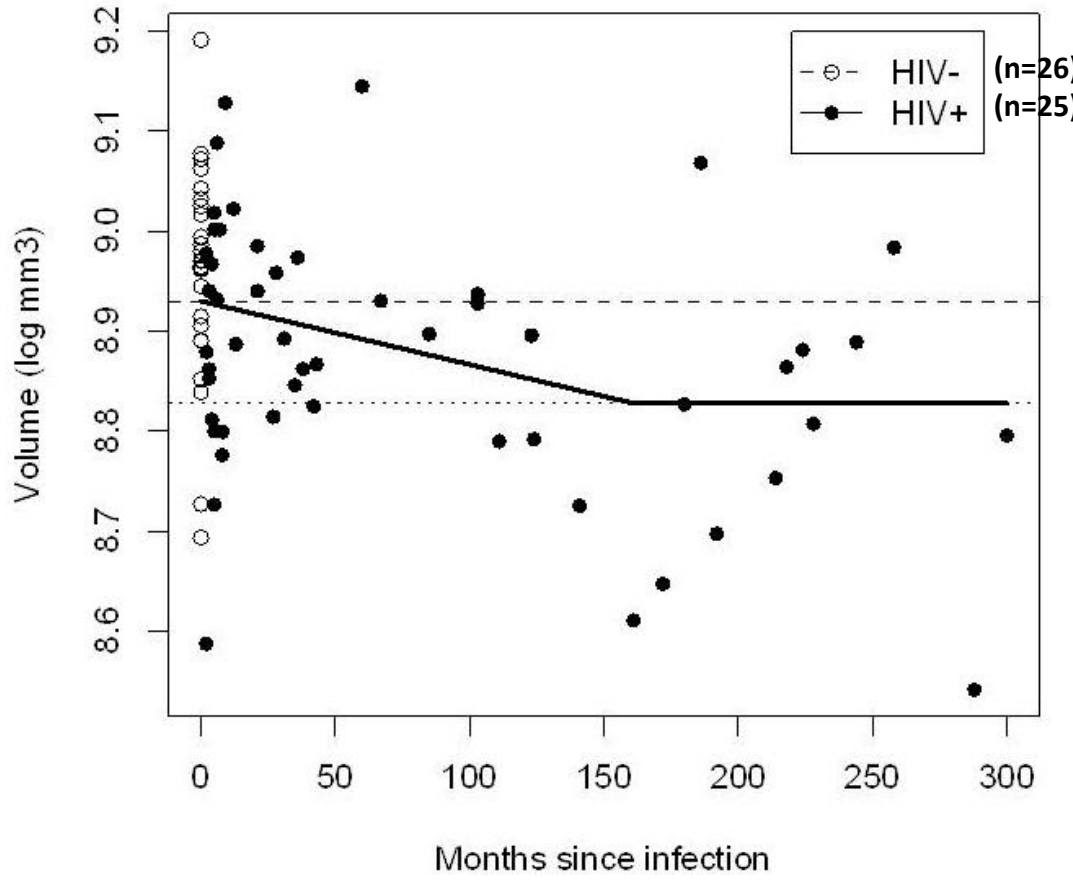
HIV and Aging Independently Reduce CBF



Ances et al., *JID*, 2010

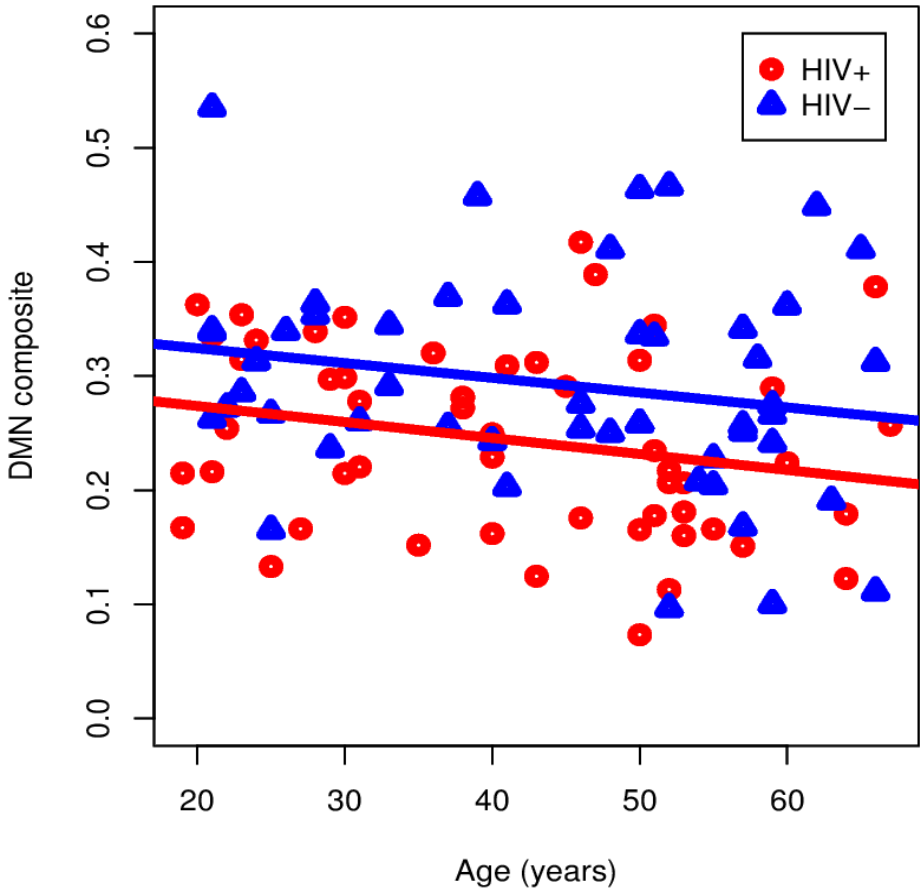
HIV and Aging Independently Reduce Brain Volumetrics

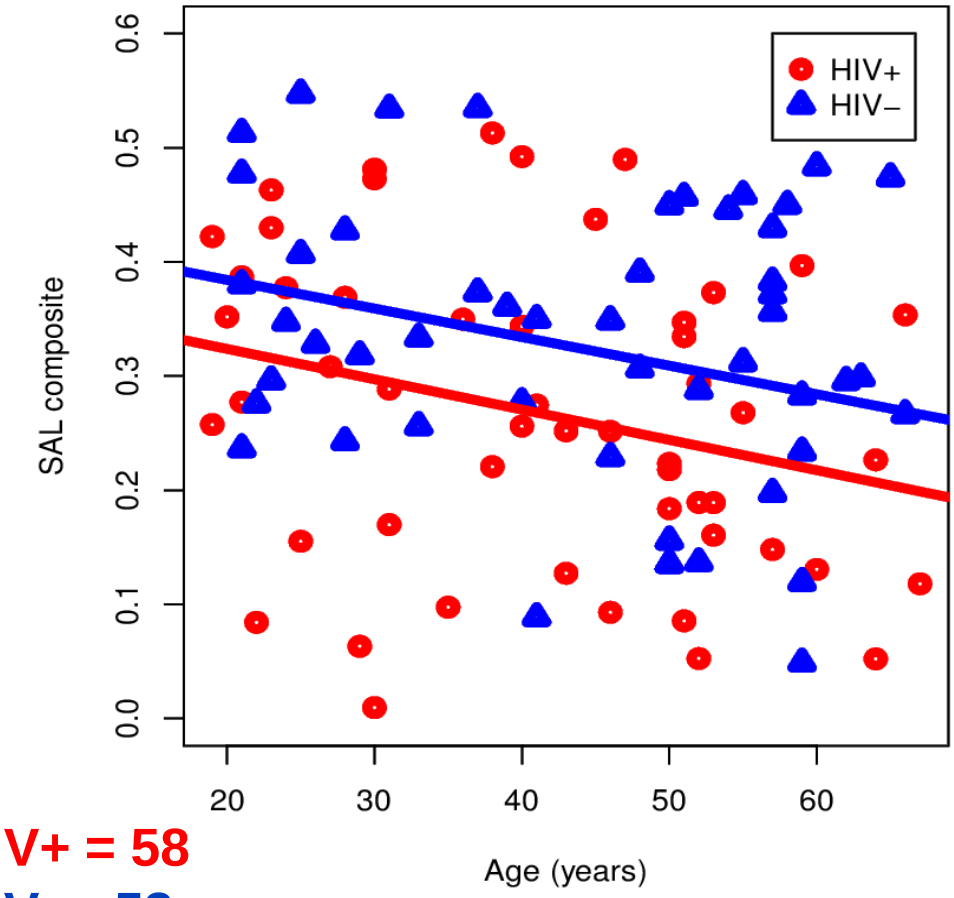




Ances et al. *JAIDS*, 2012

HIV and Aging Independently Reduce rs-fcMRI



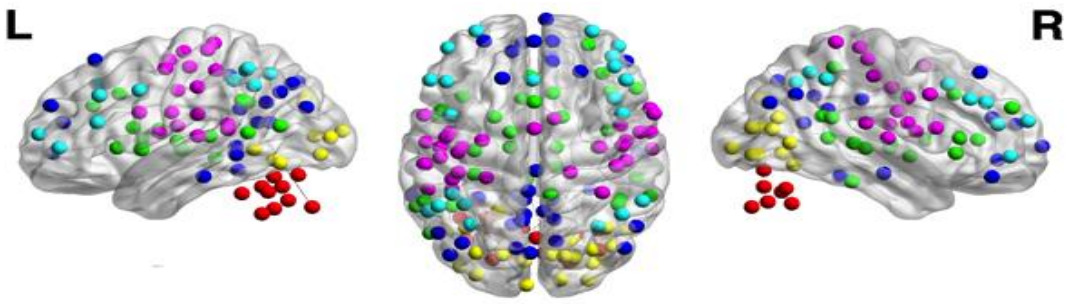


HIV+ = 58

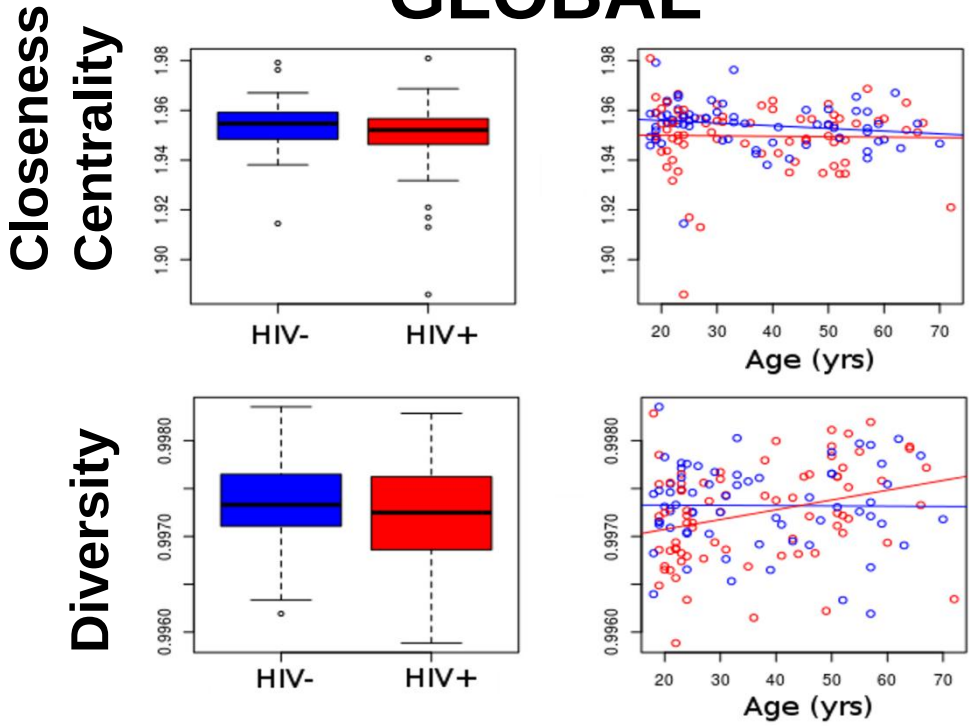
HIV- = 53

Thomas et al., *Neurology,* 2013

HIV Primarily Affects Hubs While Aging Affects Entropy at the Global and Network Levels



GLOBAL



NETWORK

Closeness centrality

		HIV	Age	HIV:Age
DMN	*p*-value	**0.005587**	0.226942	0.440119
	beta	**-0.001408**	-0.000034	-0.000174
PAR	*p*-value	**0.032704**	0.255023	0.626612
	beta	**-0.003703**	-0.000070	-0.000130
CER	*p*-value	0.286310	0.167802	*0.093663*
	beta	-0.022115	-0.000036	*0.000484*
CINGO	*p*-value	0.454033	0.582788	0.626612
	beta	-0.008279	-0.000025	0.000144
OCC	*p*-value	0.552404	0.255023	0.952956
	beta	-0.002890	-0.000175	0.000014
SMN	*p*-value	0.552404	0.255023	0.440119
	beta	-0.011797	-0.000275	0.000273

Eigenvector Centrality

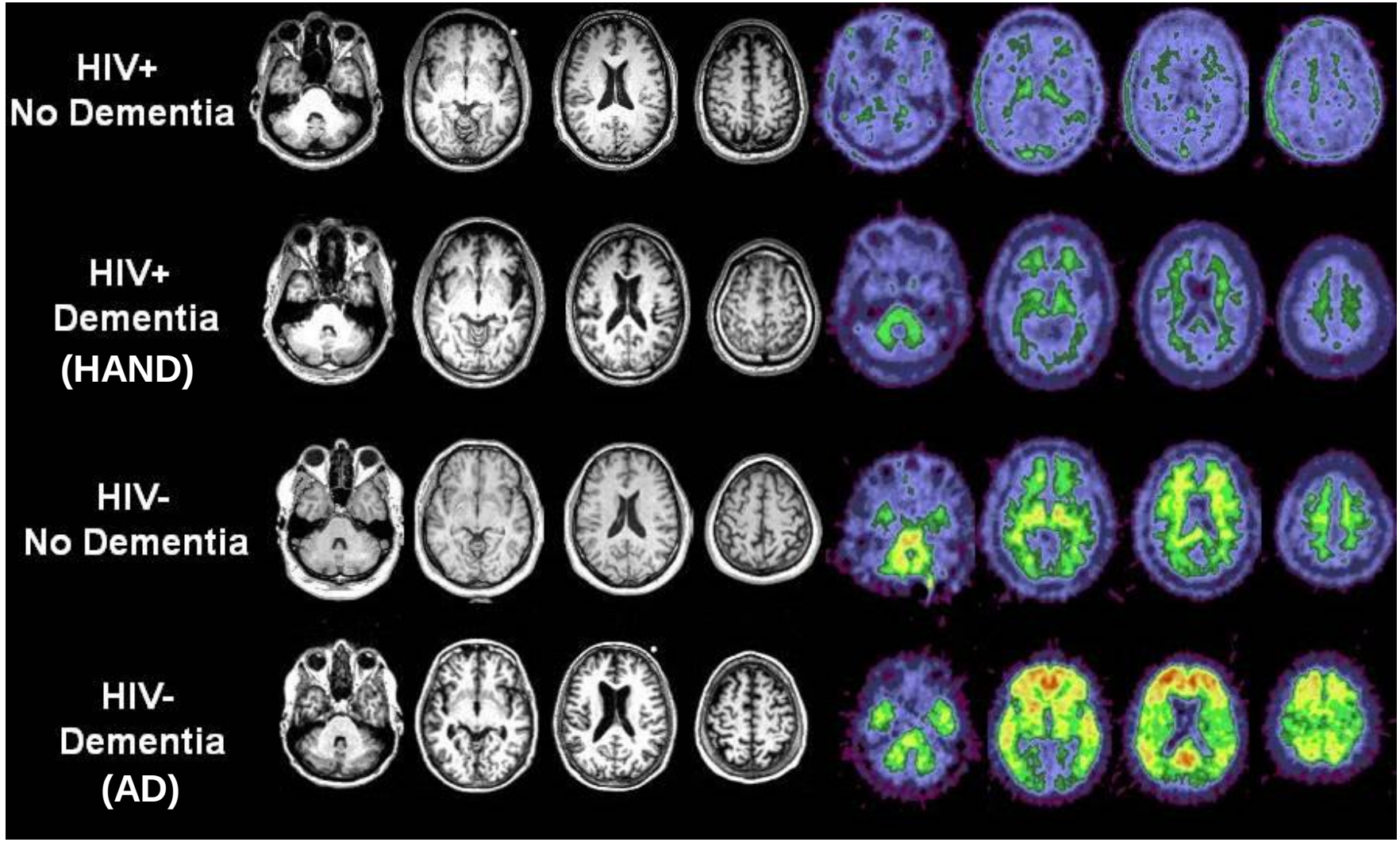
		HIV	Age	HIV:Age
DMN	*p*-value	0.754266	0.968081	0.808622
	beta	-0.007735	-0.000102	0.000187
PAR	*p*-value	0.754266	0.802798	0.808622
	beta	-0.009027	-0.000055	0.000217
CER	*p*-value	0.716851	0.802798	0.808622
	beta	0.002883	-0.000013	-0.000150
CINGO	*p*-value	0.448733	0.889757	0.808622
	beta	-0.005049	-0.000052	0.000043
OCC	*p*-value	0.273378	0.802798	0.808622
	beta	-0.006721	0.000047	0.000042
SMN	*p*-value	0.273378	0.802798	0.808622
	beta	-0.002816	0.000136	-0.000044

Diversity

		HIV	Age	HIV:Age
DMN	*p*-value	0.845908	**0.000035**	0.291414
	beta	-0.000309	**0.000014**	0.000009
PAR	*p*-value	0.773990	*0.05266136*[t]	0.883927
	beta	0.000028	*0.000006*	0.000001
CER	*p*-value	0.491484	0.263394	*0.08233318*[t]
	beta	-0.000884	-0.000015	*0.000018*
CINGO	*p*-value	0.573612	*0.05266136*[t]	*0.08233318*[t]
	beta	-0.000436	*-0.000010*	*0.000010*
OCC	*p*-value	0.491484	0.263394	*0.08233318*[t]
	beta	-0.000535	-0.000005	*0.000021*
SMN	*p*-value	0.845908	0.332862	0.187336
	beta	-0.000473	-0.000010	0.000012

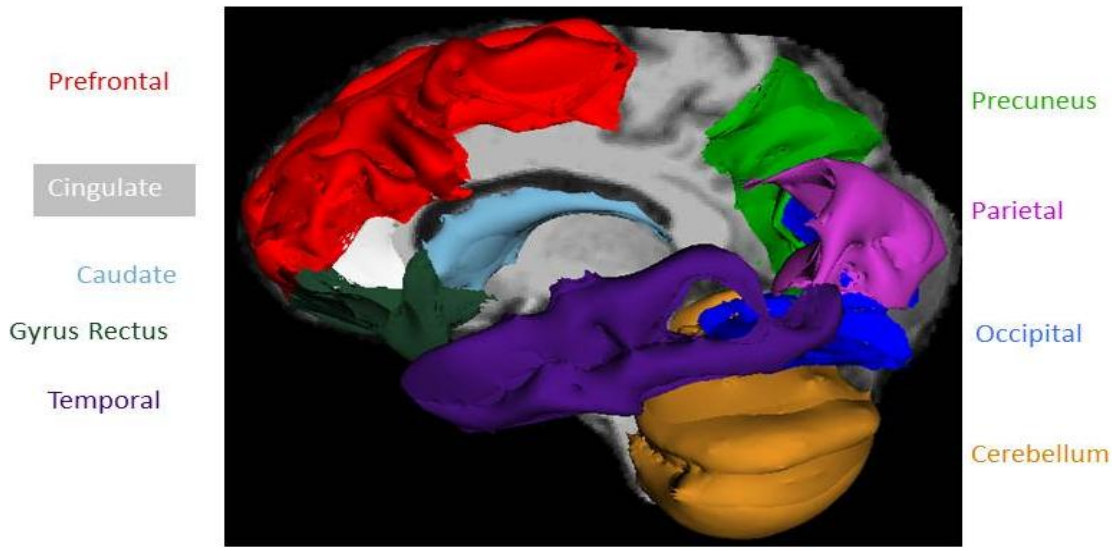
Thomas et al., *under review*

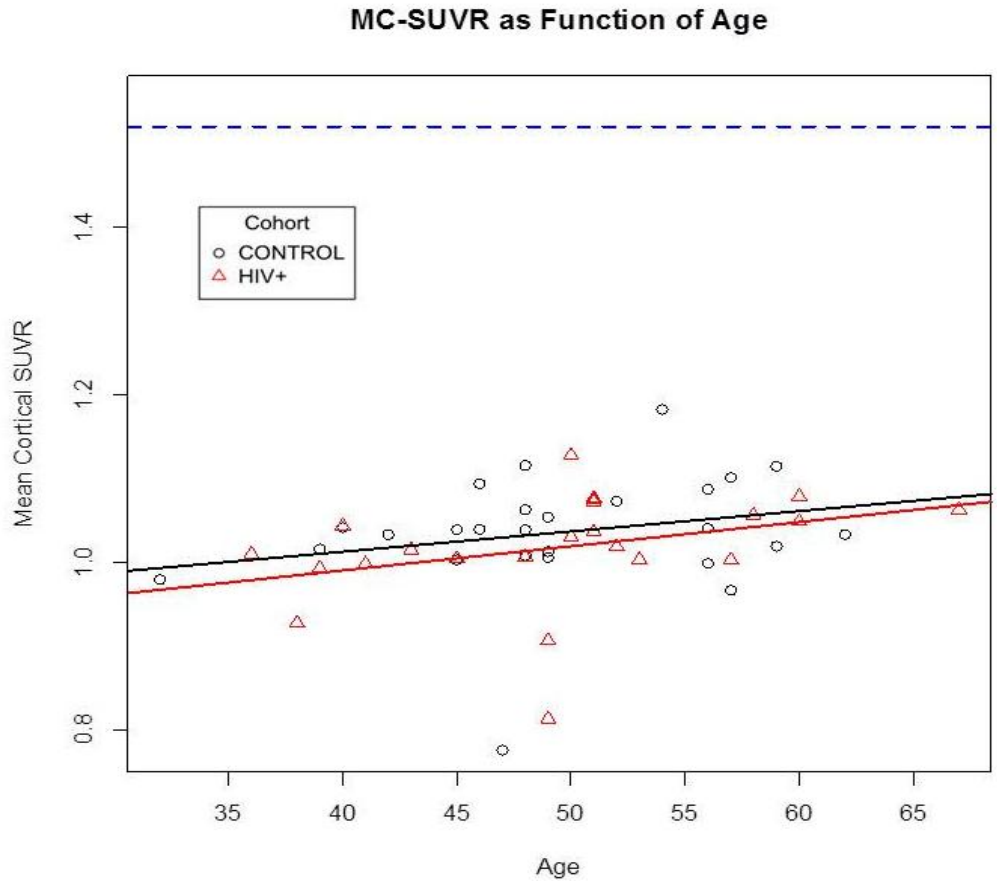
PiB Helps Distinguish AD from HAND



Ances et al. *Neurology,* 2010; Ances et al, *Arch of Neurol.,* 2012

Effects of HIV and Aging on Amyloid Deposition



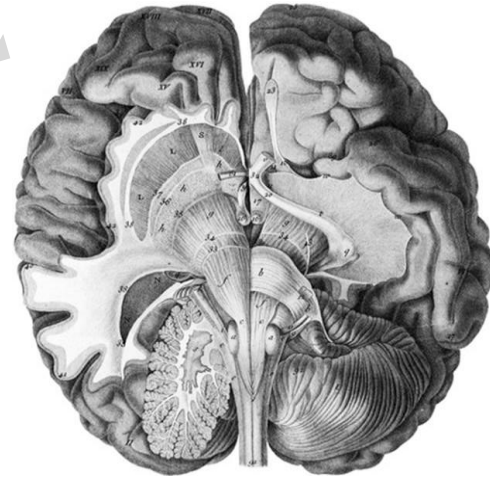


Ortega and Ances, *J Neuroimmune Pharmacol.*, 2014

Mechanisms of HIV-Related CNS Injury in the Setting of cART in Our Patient

Early impact of HIV in the CNS soon after seroconversion or "burnt out" state

Co-morbidities (substance abuse, co-infections, mood disorders)



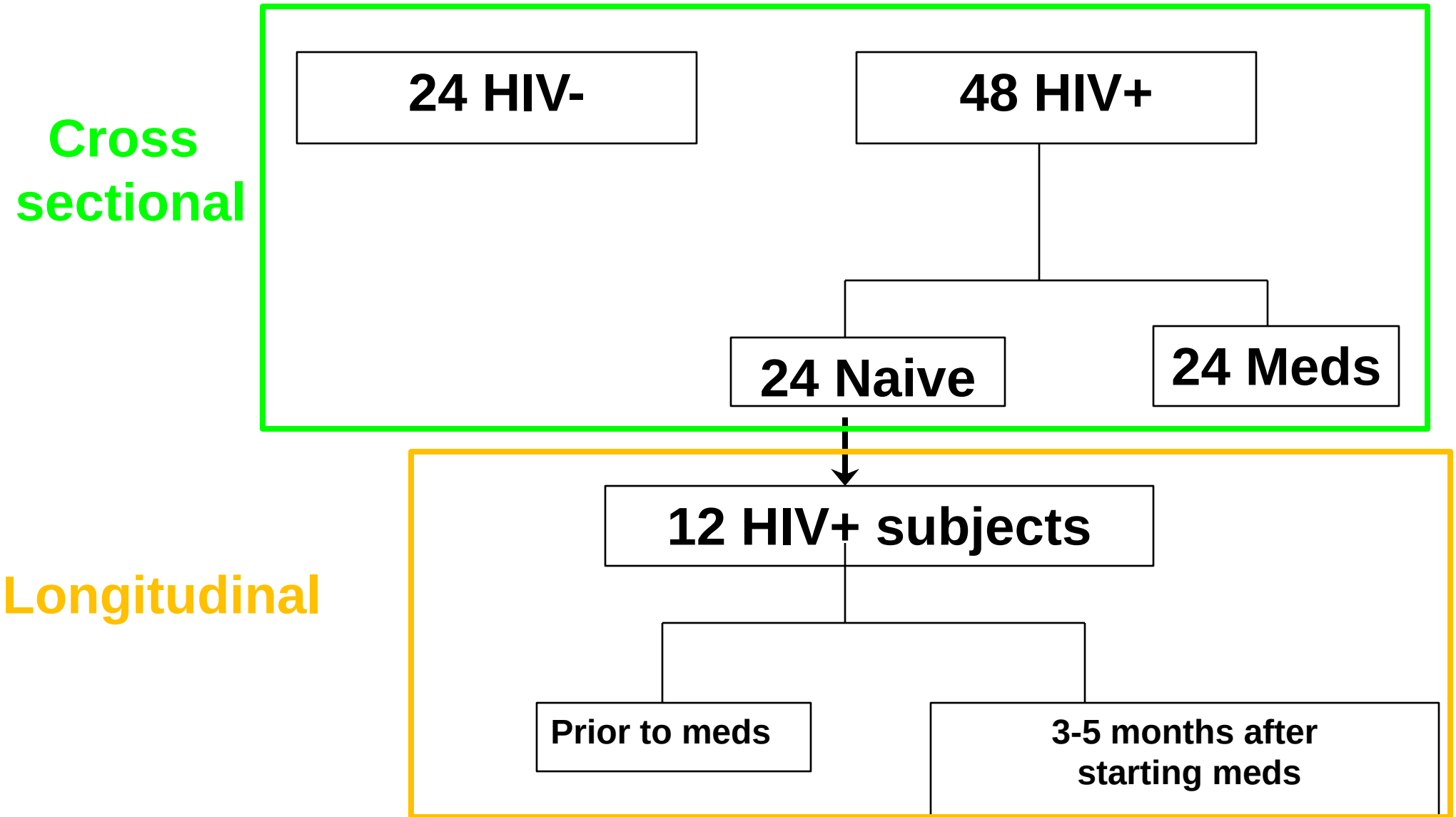
Aging

Ongoing CNS immune activation and active virus

Delayed HAART exposure or toxicity due to cART within CNS

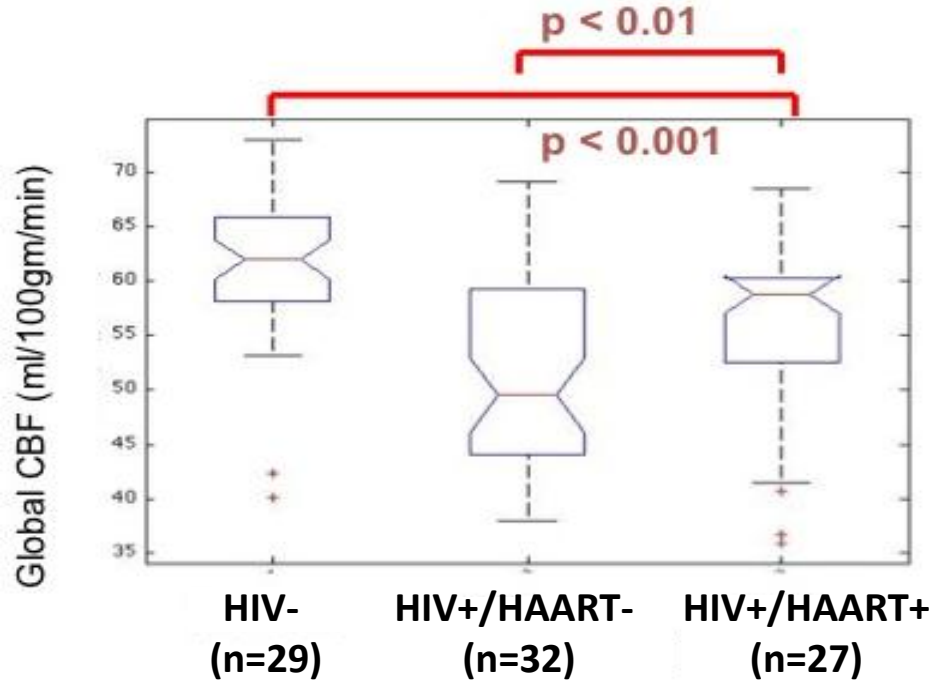
Atripla (has been on numerous combination antiretroviral therapies (cART) in the past)

Study Design for Assessing Effects of HAART on CBF

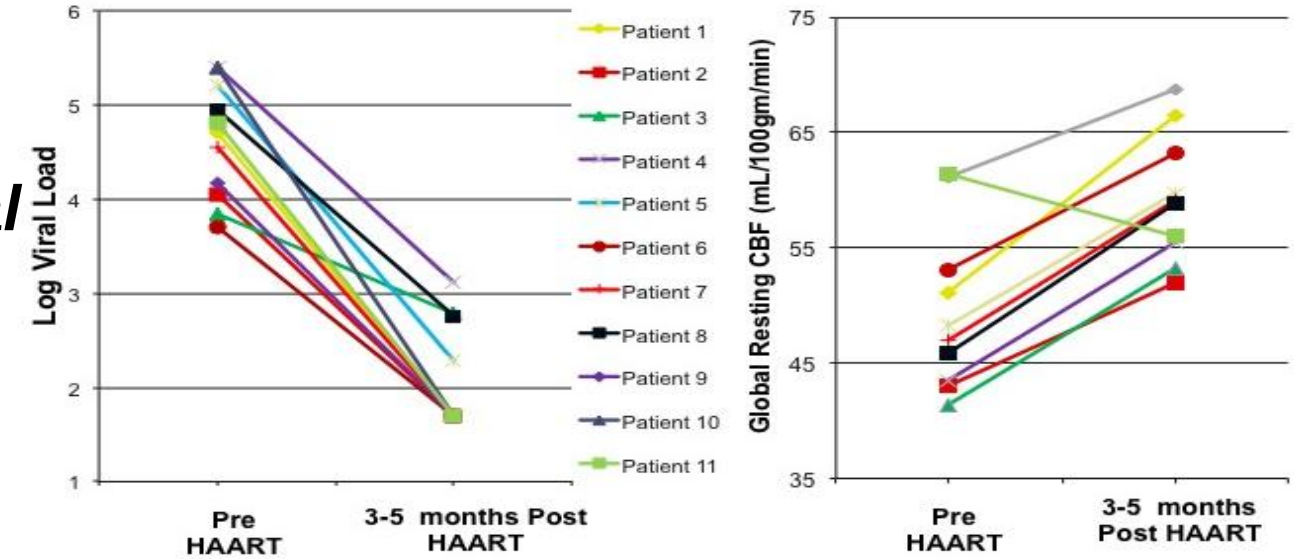


HAART Improves Resting CBF

Cross-sectional



Longitudinal



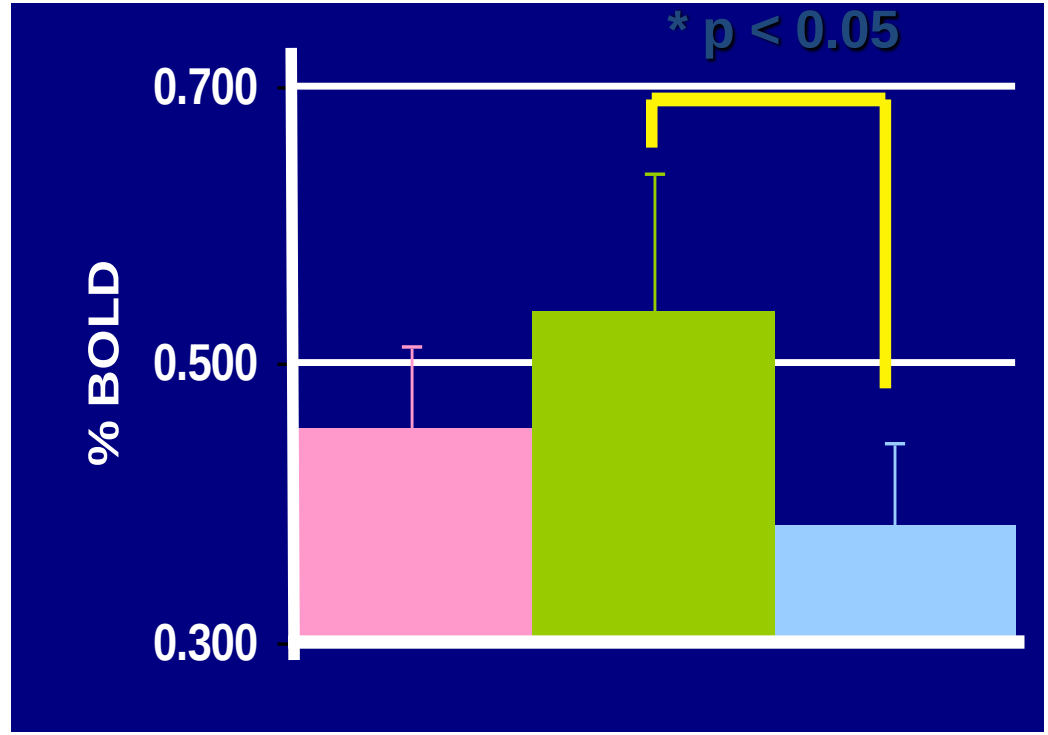
Thomas et al., *CROI,* 2012

Antiretroviral CNS Penetration-Effectiveness (CPE) Affects Neuroimaging Measures

CPE

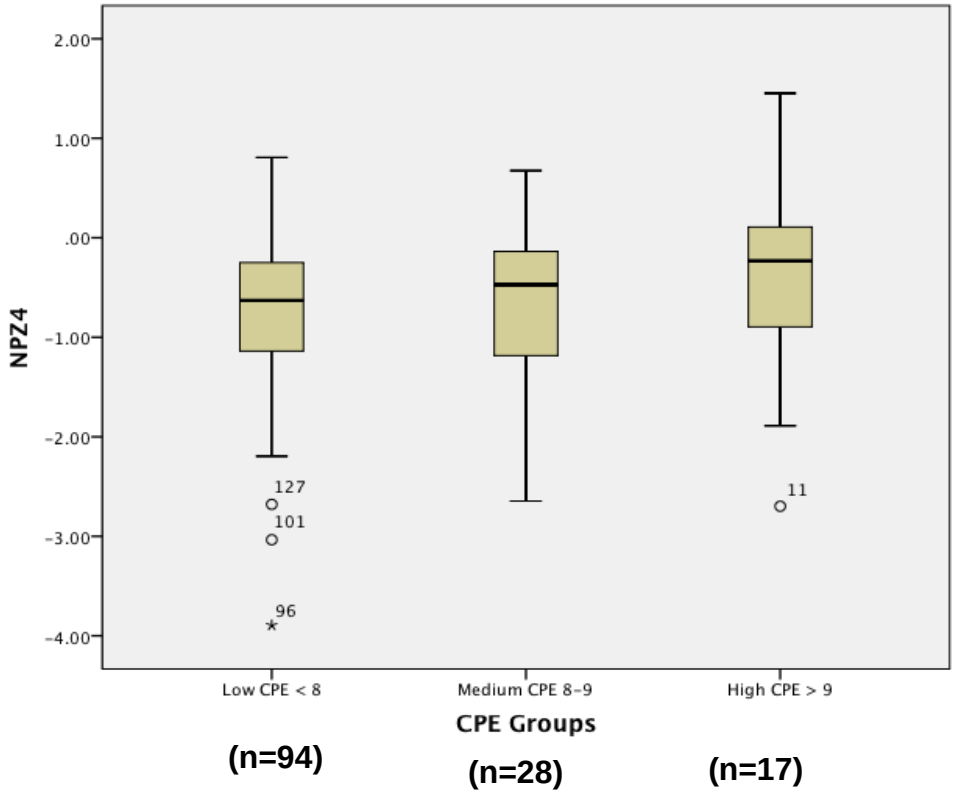
	1	0.5	0
NRTIs	Abacavir Zidovudine	Emtricitabine Lamivudine Stavudine	Didanosine Tenofovir Zalcitabine
NNRTIs	Delavirdine Nevirapine	Efavirenz	
PIs	Amprenavir-r Indinavir-r Lopinavir-r	Amprenavir Atazanavir Atazanavir-r Indinavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Fusion Inhibitors			Enfuvirtide

Letendre et al., *Arch Neurol*, 2008

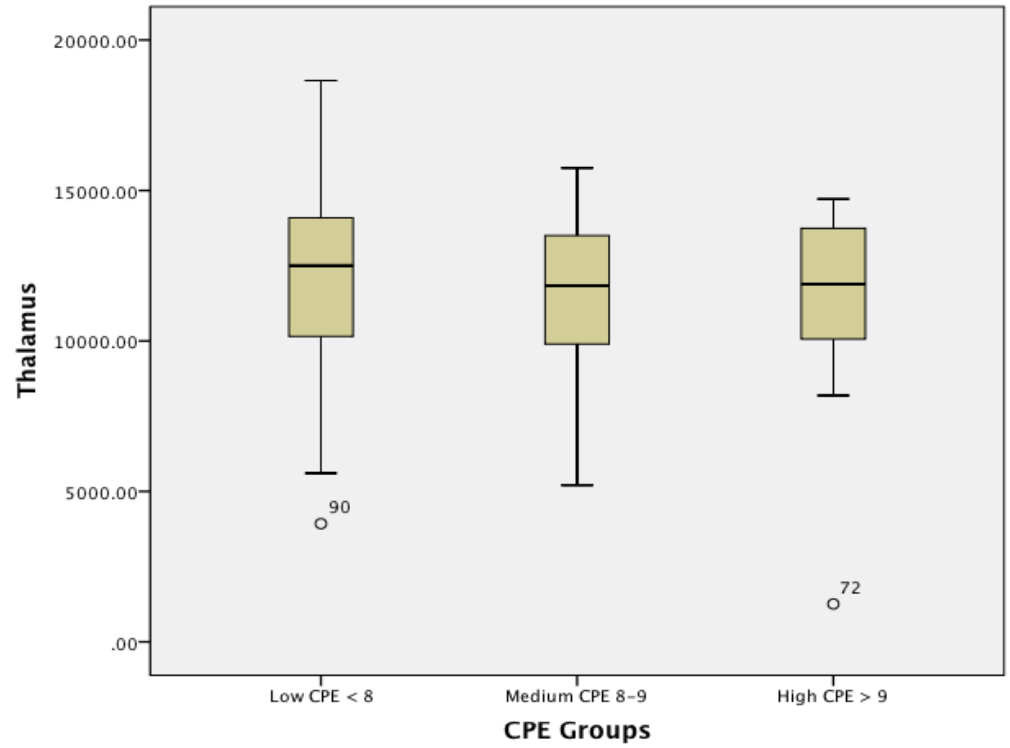


Ances et al., *J Neurovirol.*, 2008

CPE Does Not Affect Neuropsychological Performance or Brain Volumetrics



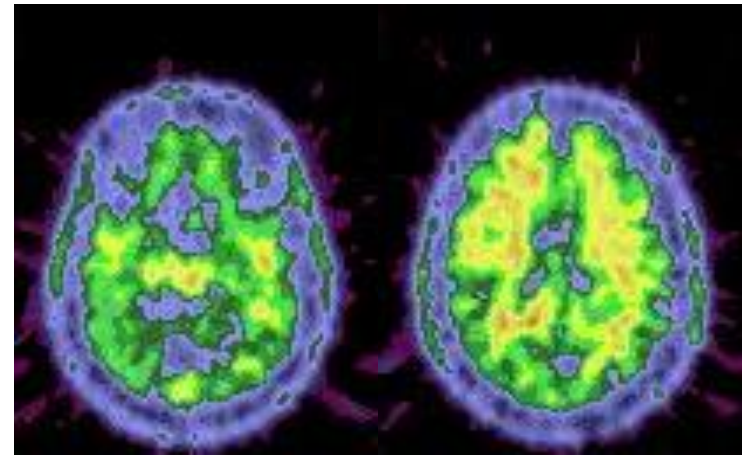
(n=94) (n=28) (n=17)



Baker et al., under preparation

- Is monocyte efficacy score (MES) is associated with neuroimaging changes?
- MES has previously shown to be associated with neurocognitive impairment (Shikuma et al, *Antiviral Therapy* 2012)

Additional Work-up of Our Patient

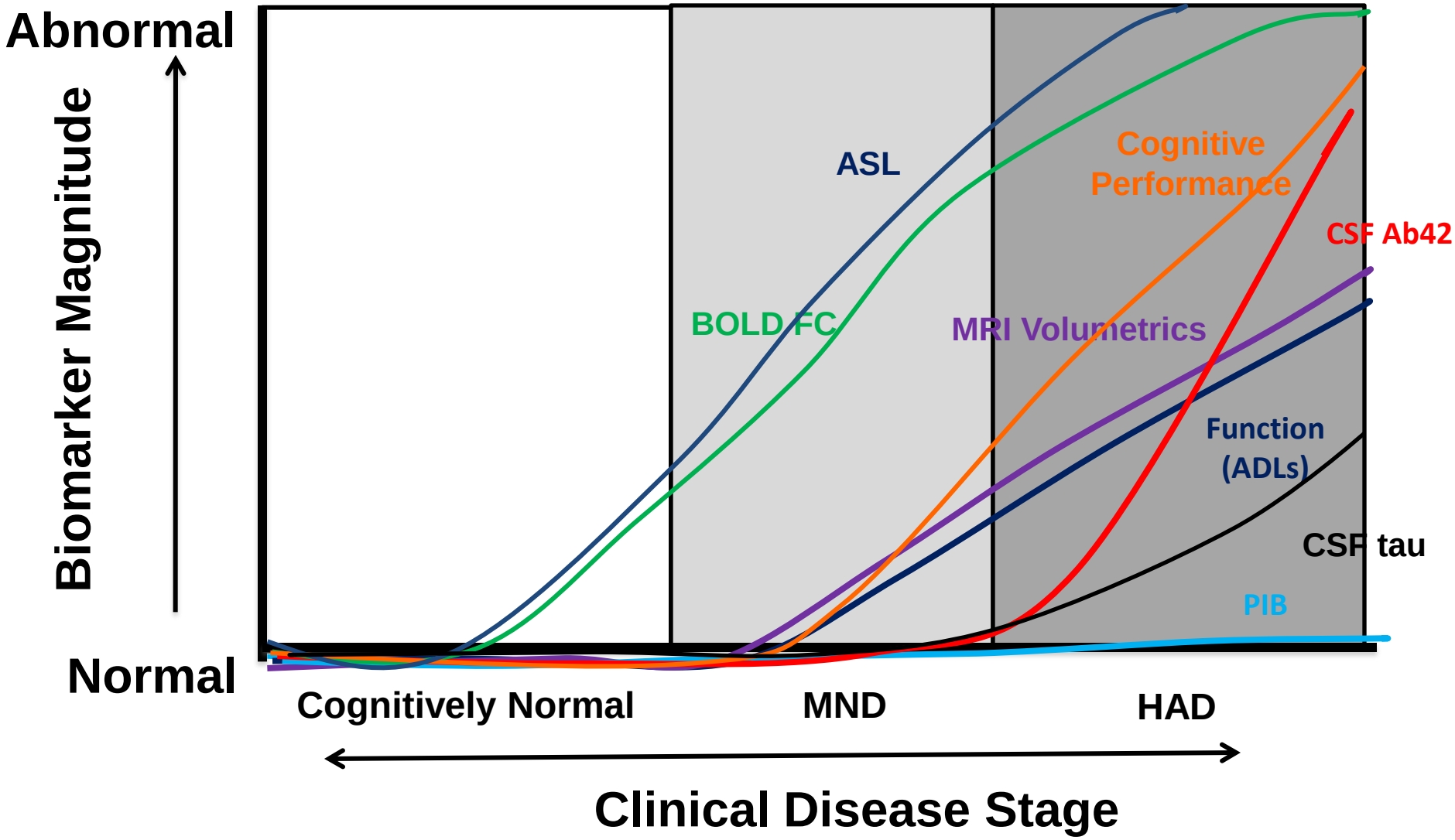


PiB: negative

Reduced global CBF

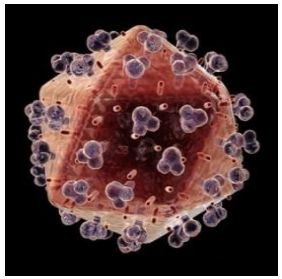
Are We There Yet?
Timeline of Biomarkers For HAND?

Temporal Progression of Biomarkers in HAND

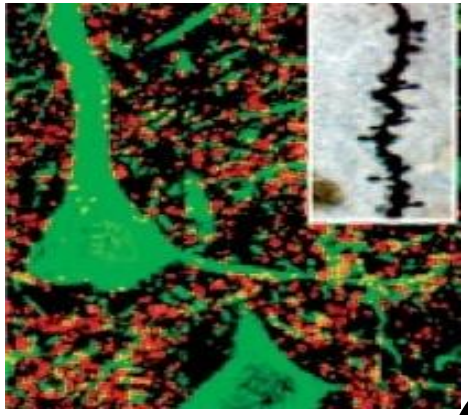


Possible Mechanism(s) for Effects of HIV and HAART in the Brain Using Neuroimaging

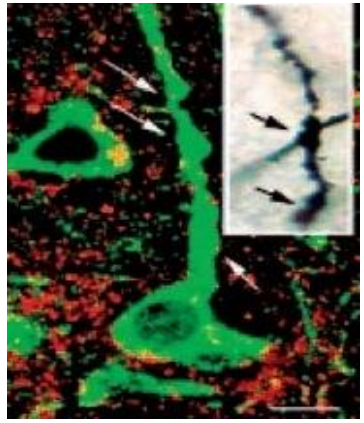
HIV



Normal Synapto-dendritic Density



Masliah et al, Ann Neurol 1997



Disruption or loss of Synapto-dendritic communication

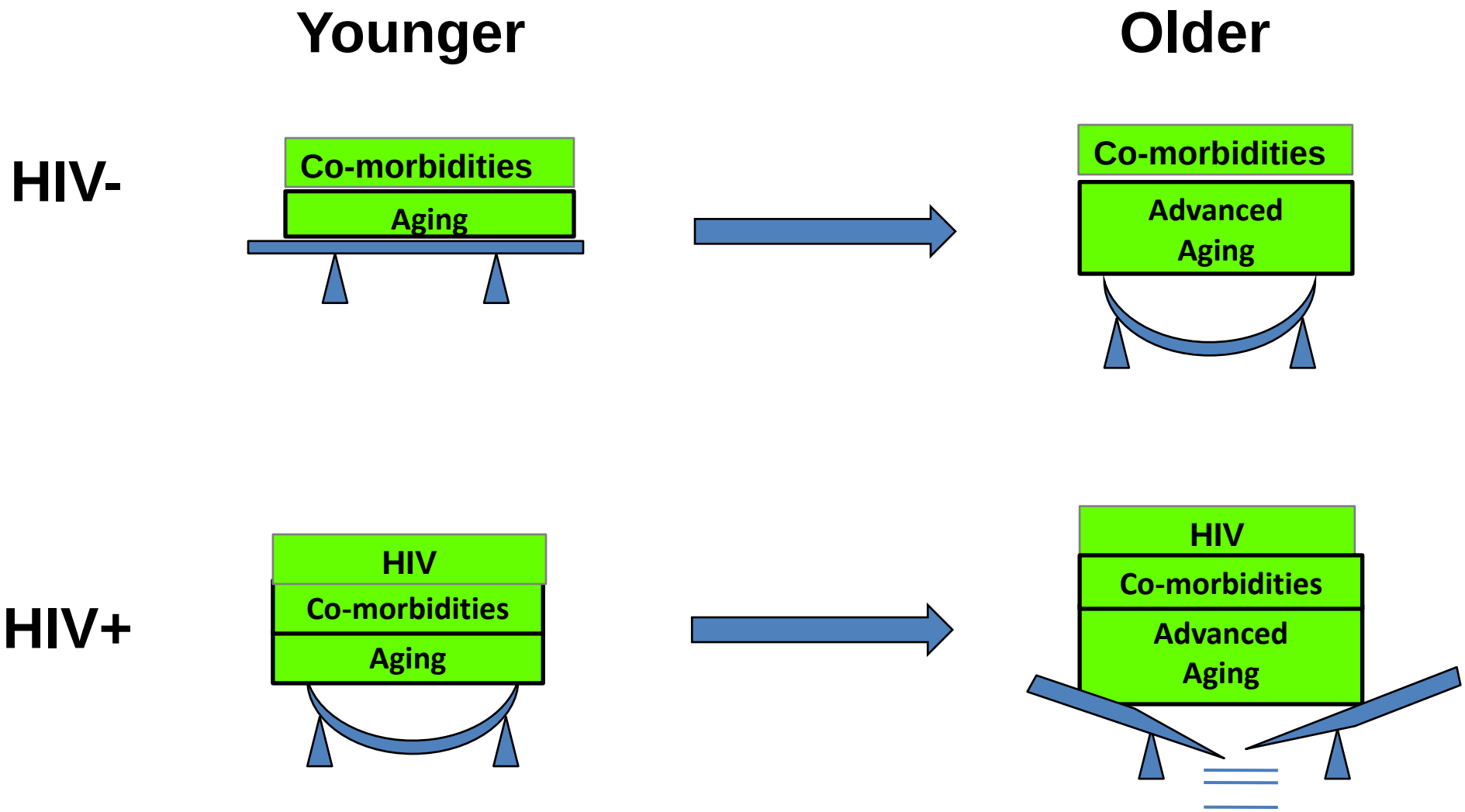
Normal CBF
Normal rs-fcMRI

Reduced CBF
Reduced rs-fcMRI

Continued low level Inflammation and virus present

HAART

HIV and Aging: Strains on the Brain



Conclusions

- Advanced neuroimaging techniques can help identify brain dysfunction due to HAND.
- Effects of HIV in the brain can be observed soon after seroconversion.
- HIV can lead to a reduction in CBF (using ASL) and rs-fc (using BOLD).
- Additional co-morbidities may affect advanced neuroimaging methods
- HIV and aging independently affect the brain (using ASL, BOLD, volumetrics).
- AD may be differentiated from HAND (using PiB).
- HAART can improve CBF (using ASL). However, CPE does not affect neuroimaging measures.
- Advanced neuroimaging techniques should be considered in the evaluation of the effects of HIV in the brain and could be included in future HAND criteria.

The Future of Neuroimaging

HIV Neuroimaging Cohorts

Name	Participants	Scanner	MRS	Vol	DTI	ASL	BOLD
CHARTER	250 HIV+	1.5 T/ 3T	X	X	X		
MACS	190 HIV+/ 150 HIV-	1.5T/3T	X	X	X		
HIV Neuroimaging Consortium	180 HIV+/ 30 HIV-	1.5 T	X	X			
WHIS	56 HIV+/ 12HIV-	3T		X	X		X
PISCES- Spudich	100 HIV+/20 HIV-	4T	X	X	X		
WUSTL- Ances	400 HIV+/ 100 HIV-	3T		X	X	X	X
Hawaii- Chang	100 HIV+/70 HIV-	3T	X	X			
UCSF- Valcour	60 HIV+/20 HIV-	3T		X	X		
Northwestern- Ragin	50 HIV+/20 HIV-	3T		X	X		X
Stanford- Pfefferbaum & Sullivan	300 HIV+/100 HIV-	1.5 T		X	X		
UCSF VA- Meyerhoff	50 HIV+/ 30 HIV-	1.5T		X			
Brown- Cohen	100 HIV+ /50 HIV-	3T		X	X		
ANRS CO3 Aquitaine	215 HIV+	1.5T		X	X		

- **Limitations: few using advanced neuroimaging methods, few are longitudinal, and few have HIV- controls**

AIDS Clinical Trial Group (ACTG) 5310

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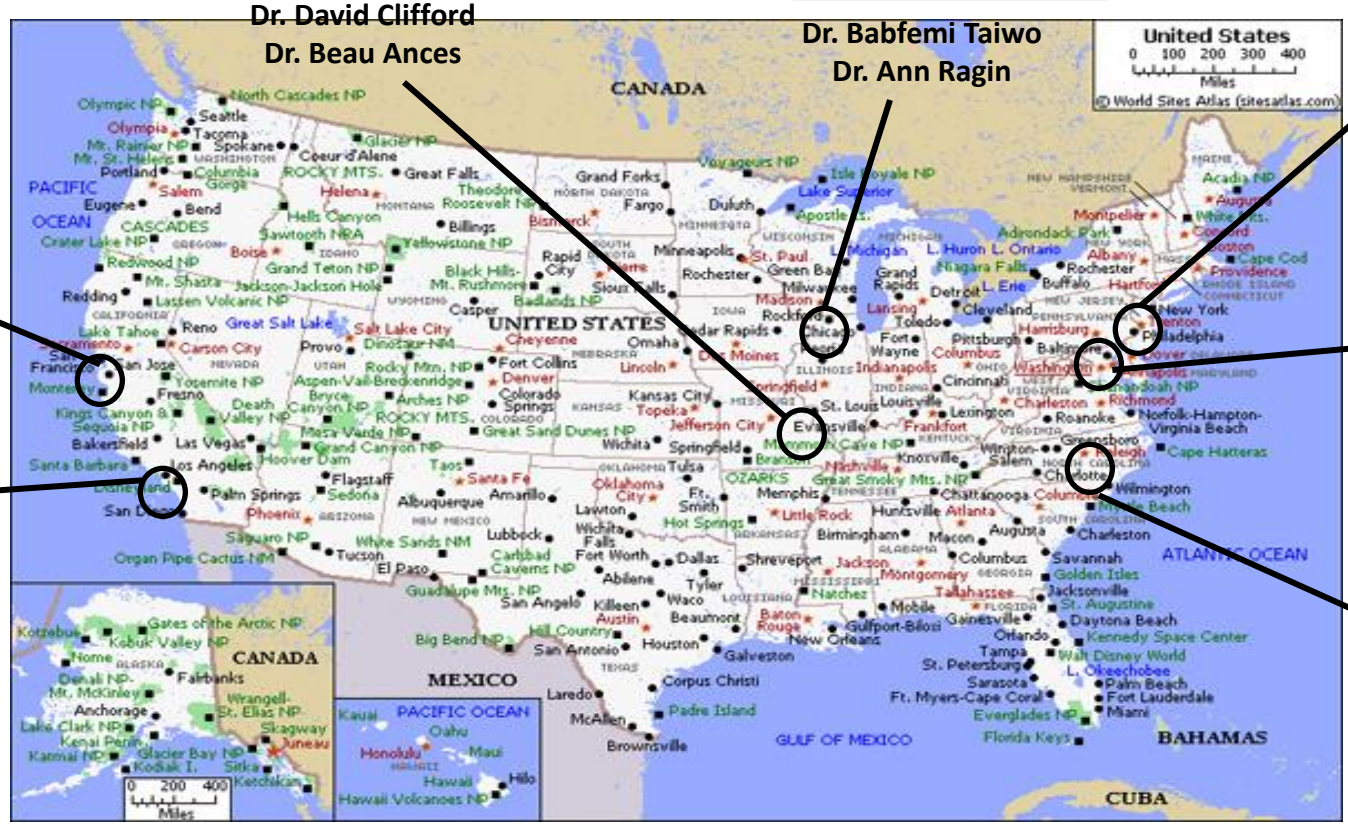
Dr. Beau Ances

Northwestern University Feinberg School of Medicine

Dr. Babfemi Taiwo
Dr. Ann Ragin

UCSF University of California San Francisco

Dr. Victor Valcour
Dr. Diane Havlir



Dr. Pablo Tebas
Dr. Dennis Kolson

Johns Hopkins Medicine
The Johns Hopkins Hospital

Dr. Ned Sacktor

UCLA David Geffen School of Medicine

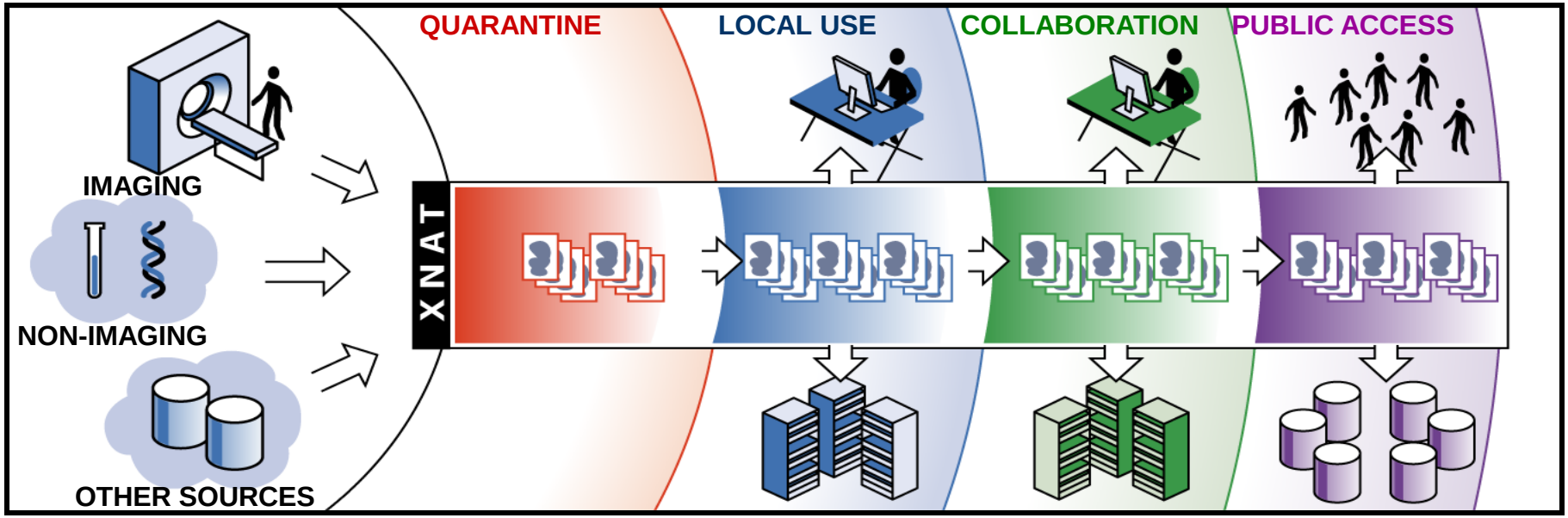
Dr. Judith Currier
Dr. JJ Wang

UNC School of Medicine

Dr. Kristine Patterson
Dr. Kevin Robertson

- Participants: 1 “phantom” subject at all 7 sites and 9 HIV+ patients from 7 sites
- Neuropsychological performance testing and advanced MRI (Volumetrics, ASL, and BOLD) obtained at all 7 sites.

Central Neuroimaging Data Archive (CNDA) at WUSTL



https://cnda.wustl.edu

- Allows for access to national and international data (i.e. DIAN)
- Can handles longitudinal studies with multiple biomarkers
- Pipelines available for processing of advanced neuroimaging methods

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  - Jodi Heaps (UMSL)

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  - Tammie Benzinger MD, PhD
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  - Alison Goate PhD
  - Randall Bateman MD

- **Collaborators**
  - Robert Paul PhD- UMSL
  - Serena Spudich MD- Yale
  - Victor Valcour MD- UCSF
  - Dan Stein MD- Capetown, SA
  - John Joska MD- Capetown, SA
  - Turner Overton MD- UAB
  - Sarah Cross MD- Vanderbilt
  - David Hass PhD- Vanderbilt

Thank you for your attention

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ances neuroimaging

http://neuro.wustl.edu/research/researchlabs/anceslaboratory.htm

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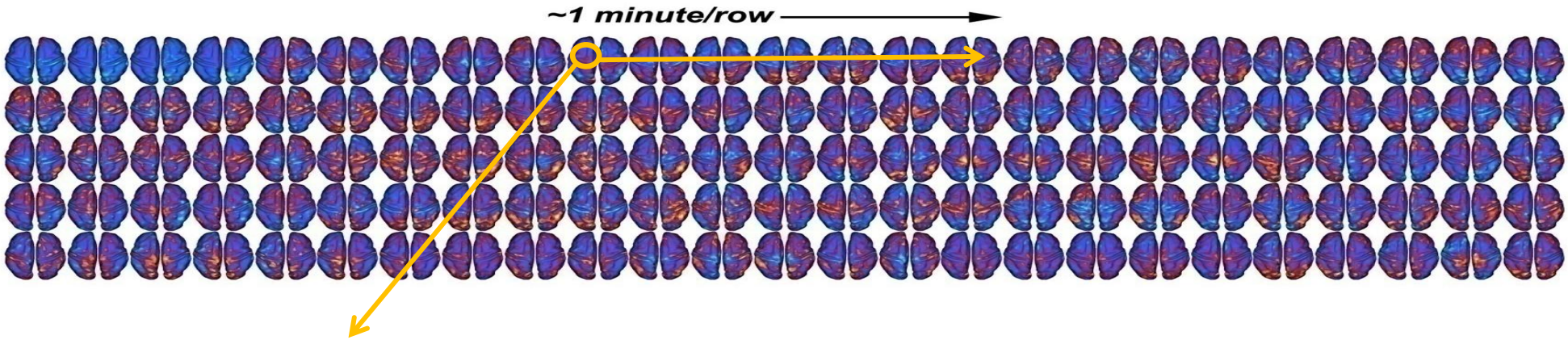
bances@wustl.edu

(314) 747- 8423

Analysis of the Restless Brain

A.



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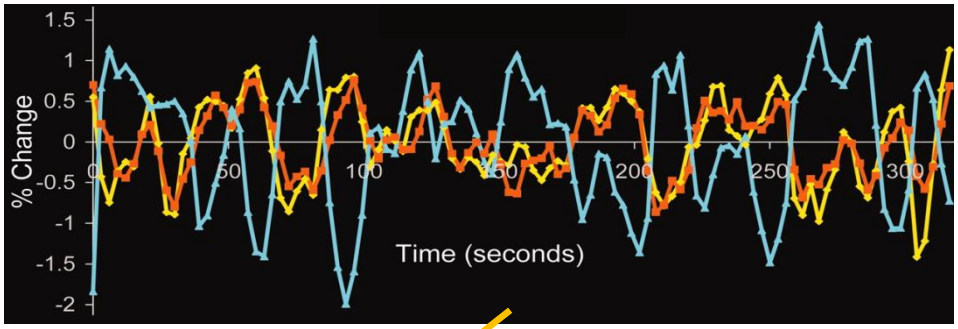

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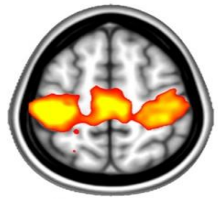
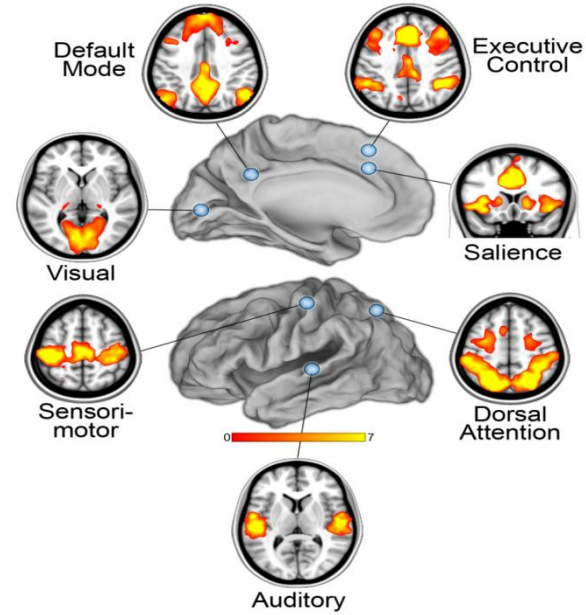


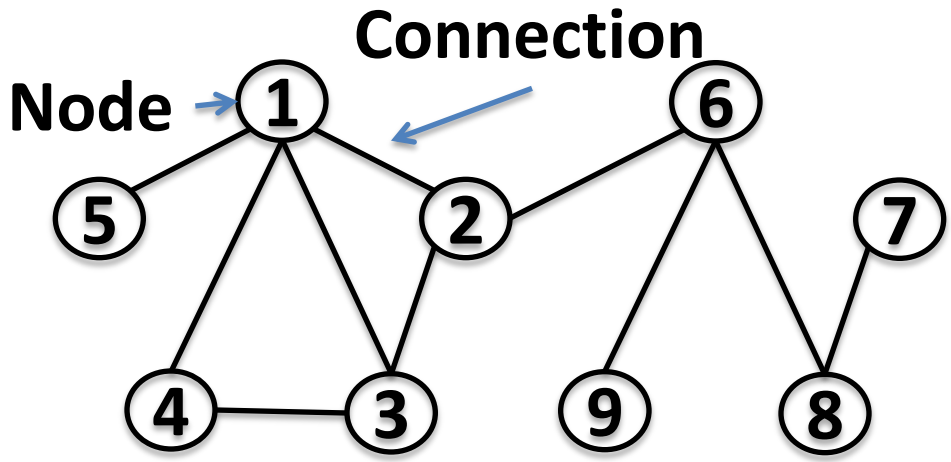
Sensorimotor

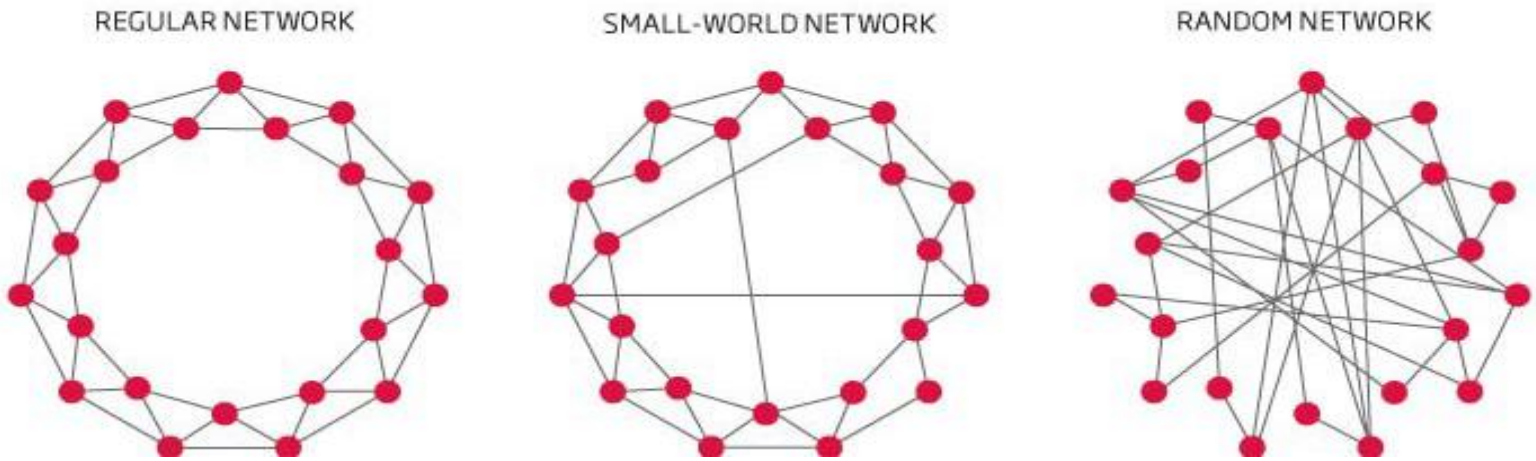
D.



Modified from Raichle, *Brain Connectivity*, 2011

Graph Theory 101

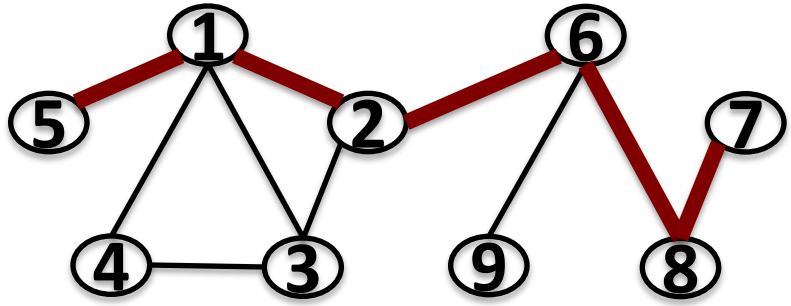




Bullmore and Sporns, *Nat Neurosci,* 2009

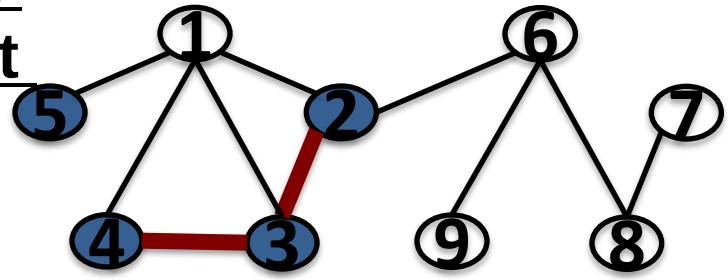
Graph Theory 101

Path Length



Path Length (*L*) from 5 to 7 = 5

Clustering Coefficient



Existing Connections between Neighbors / Possible Connections between Neighbors

$$CC_1 = \frac{2}{\binom{4}{2}} = \frac{2}{6} = .33$$

Neighbors of 1 in blue = 4 Actual connections in red = 2

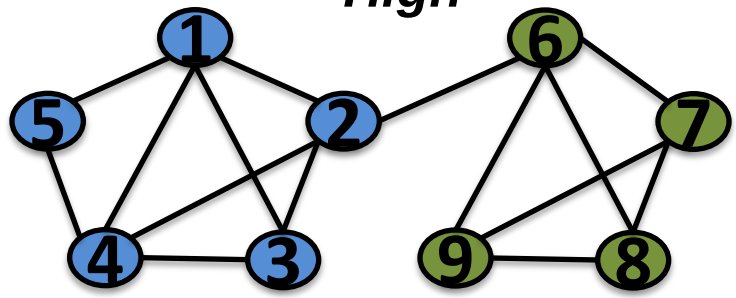
Small Worldness

$$S = \frac{C/C^0}{L/L^0}$$

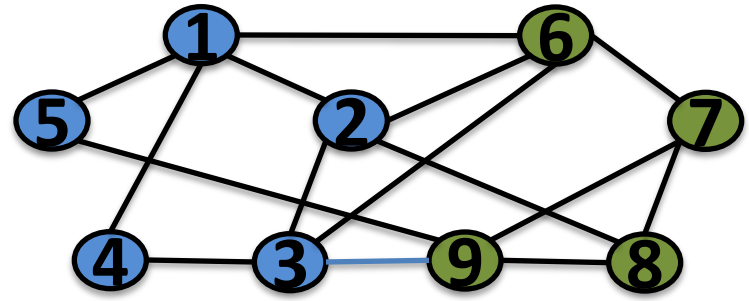
S> 1

Modularity

High



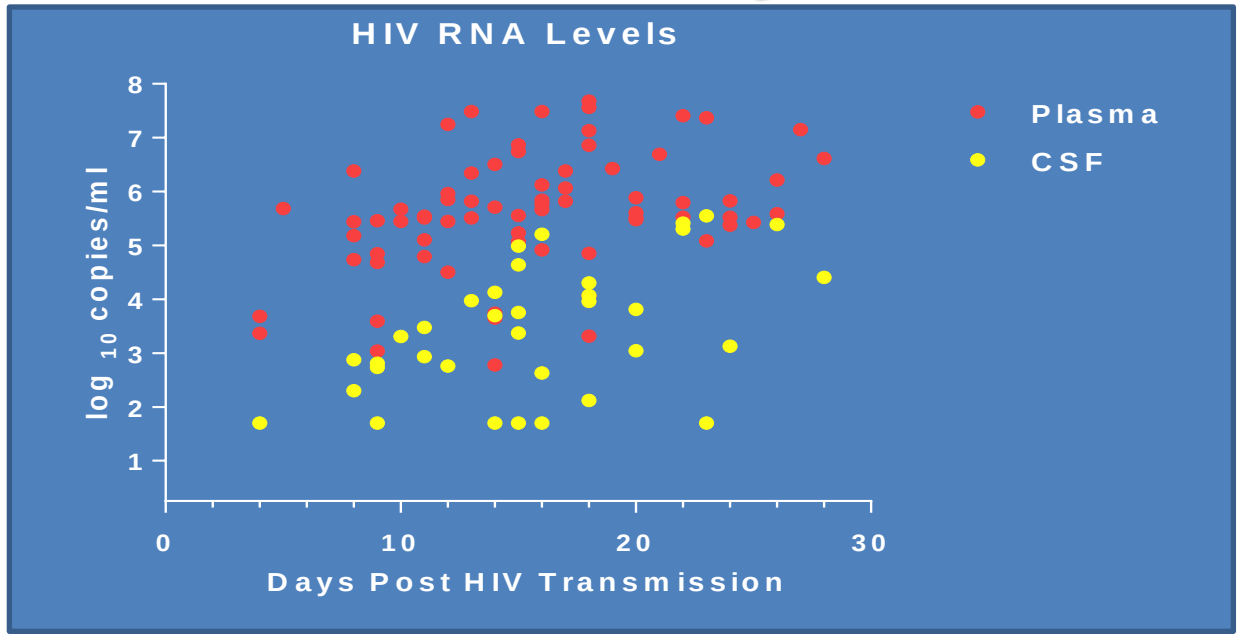
Low



Potential HIV Reservoir in the CNS

- The detection of compartmentalized cerebrospinal fluid (CSF) HIV variants with respect to blood suggests existence of a CNS reservoir of HIV infection.
- Compartmentalized CNS HIV has been detected in early infection, though its origin is unknown.

Thai Primary HIV Cohort

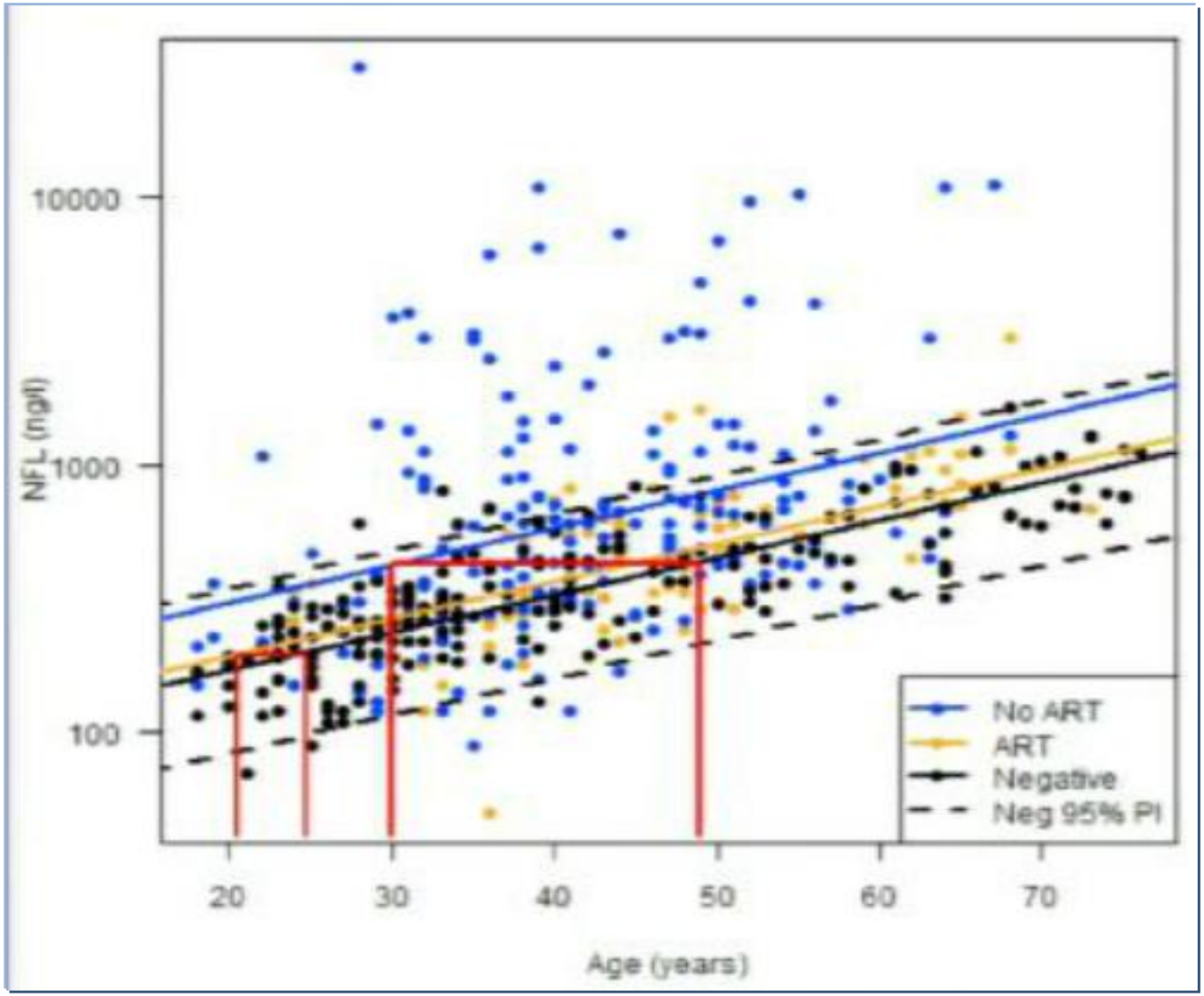


Spudich et al., *CROI*, 2013

Implications for the Clinic

- Viral seeding of the CNS occurs soon after infection.
- Attention to the virus in CNS remains critical as a reservoir can develop.
- Early intervention with anti-retroviral therapy (ART) may be beneficial but additional longitudinal studies needed.
- Lumbar puncture (LP) should be considered when new neurologic symptoms are present in a HIV+ patient, even with good virological control in the plasma.
- Other etiologies besides virological escape may account for neurocognitive impairment.

HIV and Aging Independently Reduce NFL



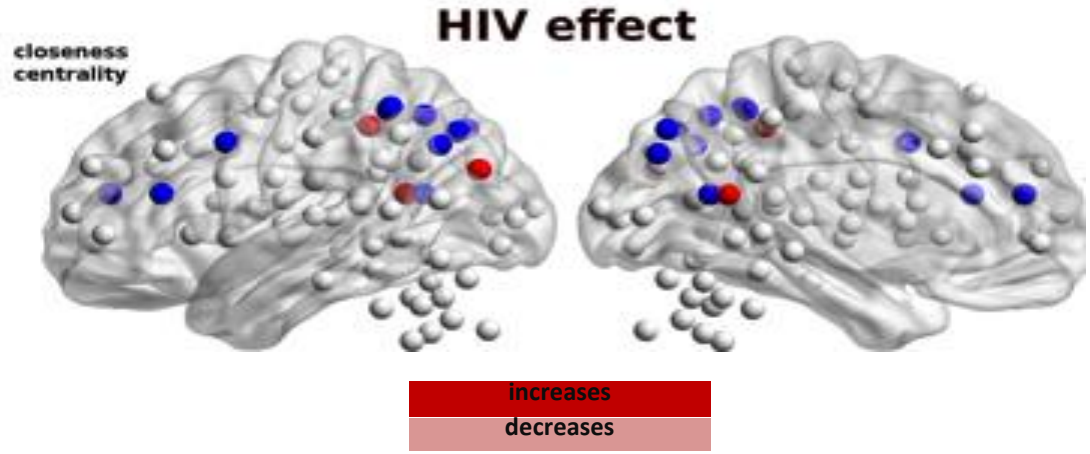
Krut et al., *CROI*, 20

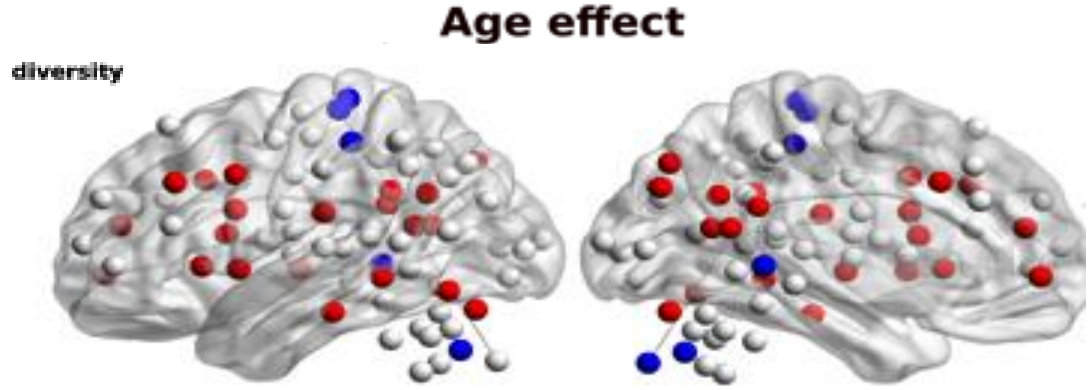
CNS Penetration-Effectiveness (CPE) Ranks

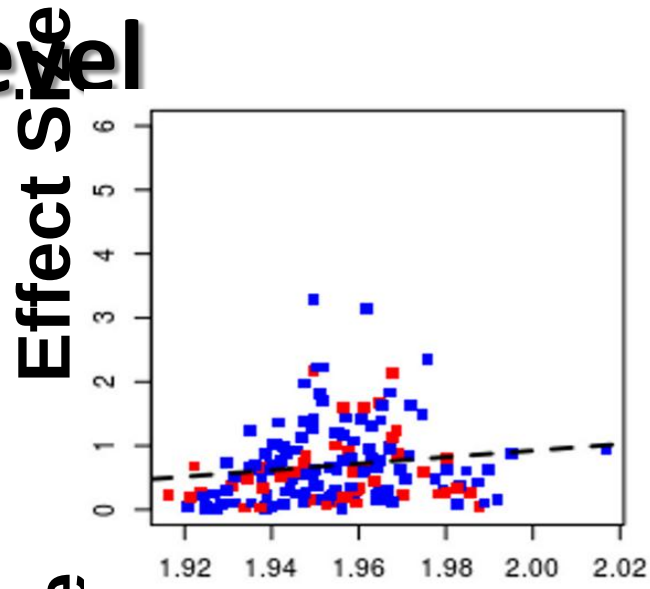
	4	3	2	1
NRTIs	Zidovudine	Abacavir Emtricitabine	Lamivudine Stavudine	Didanosine Tenofovir Zalcitabine
NNRTIs	Nevirapine	Delavirdine Efavirenz	Etravirine	
PIs	Indinavir-r	Darunavir-r Fosamprenavir-r Indinavir Lopinavir-r	Atazanavir Atazanavir-r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Entry Inhs	Vicriviroc	Maraviroc		Enfuvirtide
Integrase Inhs		Raltegravir		

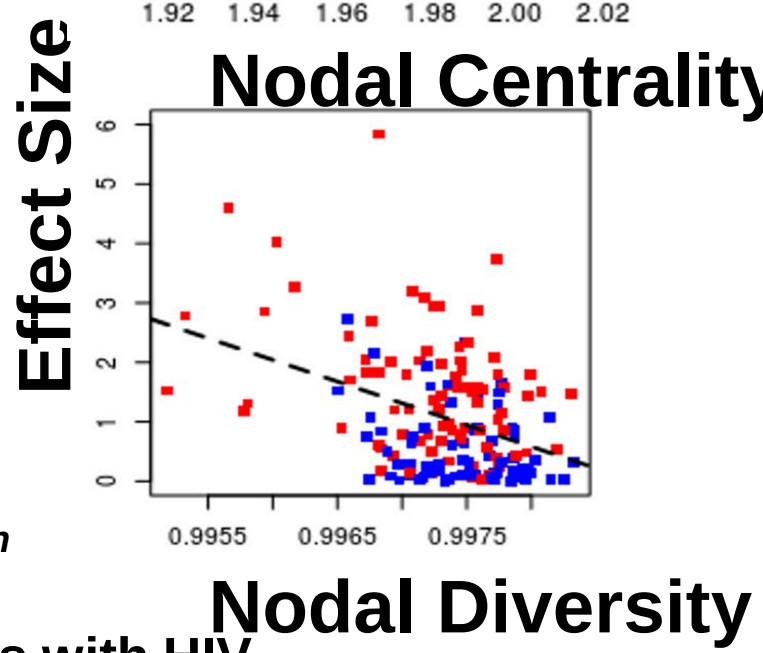
Letendre et al., *Top in HIV M*

HIV Primarily Affects Hubs While Aging Affects Entropy: Node Level





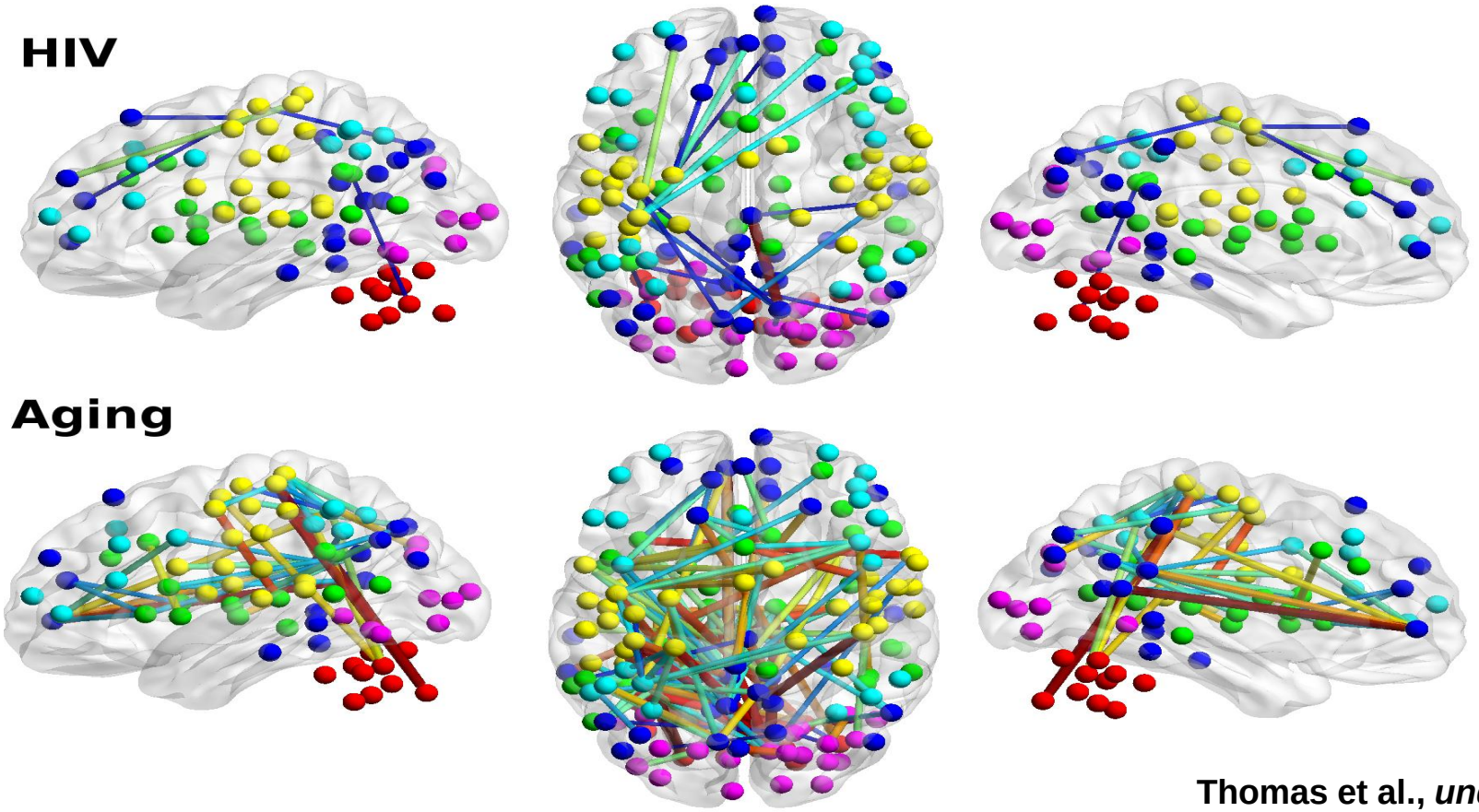




Thomas et al., *under preparation*

- Nodes with higher centrality had greater decreases with HIV.
- Nodes with lower diversity had greater increases with Age.

Effects of HIV and Aging on Brain Topology Are Similar for Edge Weights



Thomas et al., *under preparation*

- Changes in edge weight correspond to areas affected by HIV effect on closeness centrality
- Patterns of edge weight changes (increases and decreases) may explain diversity changes seen with Aging