

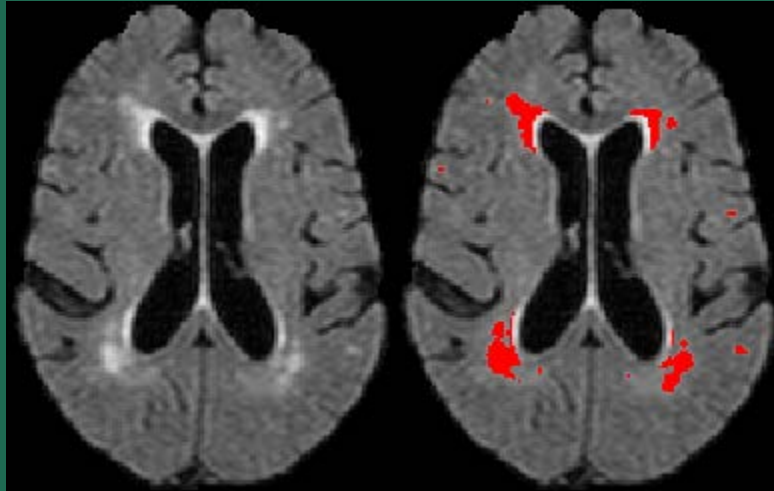
# Imaging methods to understand the impact of CVD on age related cognitive decline

Clinton Wright, MD, MS  
Evelyn F. McKnight Chair for  
Learning and Memory in Aging

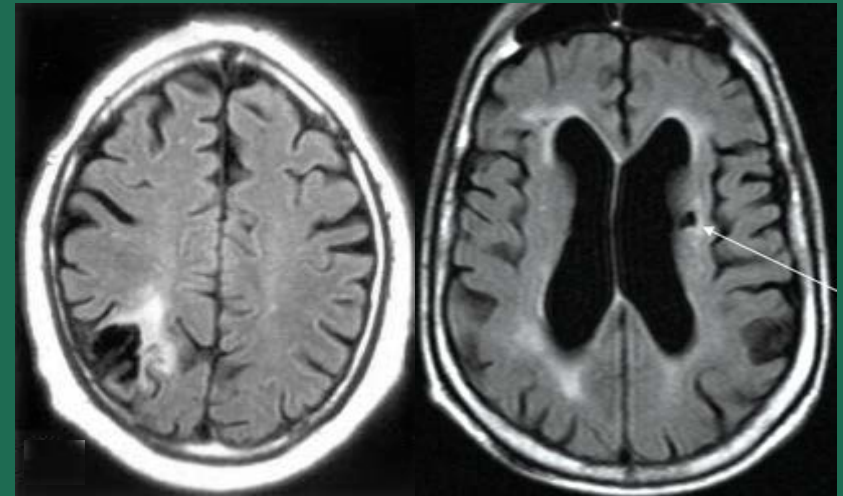
April 30, 2015  
University of Miami

# Subclinical Vascular Brain Damage

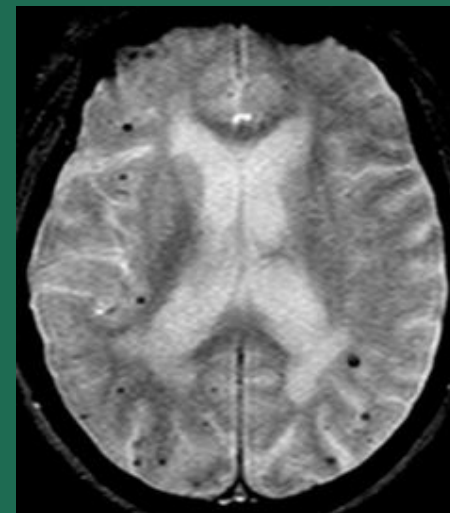
white matter  
hyperintensities



subclinical Infarcts



brain atrophy



microbleeds

# Population Prevalence of Subclinical Infarction (3 mm+)

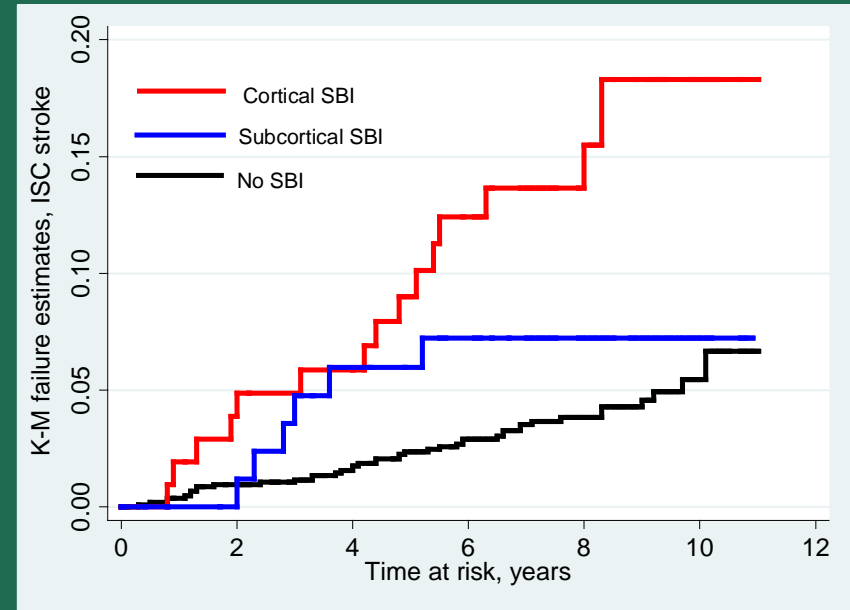
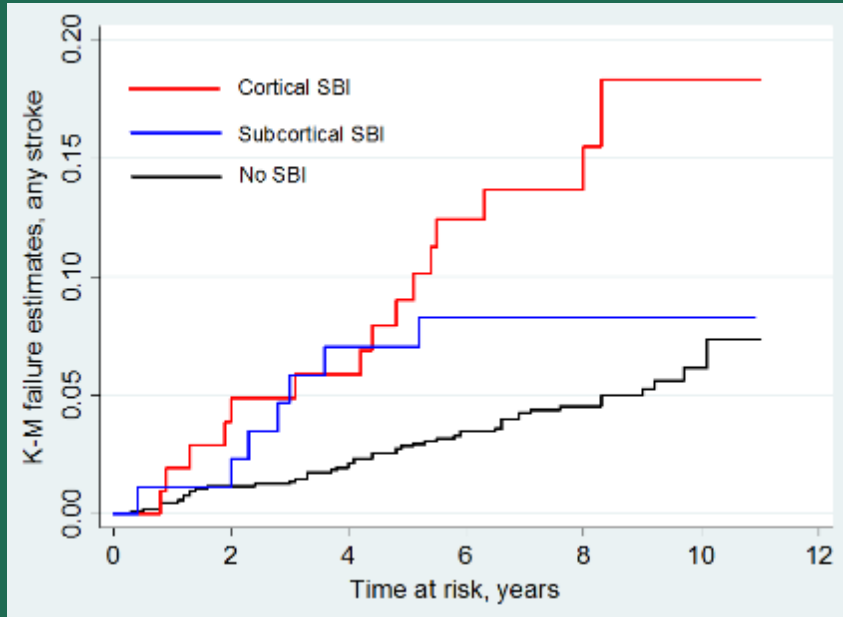
<b>Study</b>	<b><u>% Prevalence for SCI</u></b>		<b>Estimated US population 1998</b>	<b>Estimated US SBI Population Prevalence (N)</b>
	<b>Age</b>	<b>Prevalence (%)</b>		
ARIC	55-64	11%	22,989,000	2,528,790
CHS	65-69	22%	9,515,000	2,093,300
	70-74	28%	8,780,000	2,458,400
	75-79	32%	7,238,000	2,316,150
	80-85	40%	4,748,000	1,899,200
	85+	43%	4,054,000	1,743,220
<b>TOTAL</b>				<b>13,039,070</b>

# Subclinical Infarction in Northern Manhattan, USA

Characteristics	No. (%)
Side	
Left	99 (45.6)
Right	117 (54.2)
Size	
Small ( $\leq 1$ cm)	178 (82.4)
Large ( $> 1$ cm)	38 (17.6)
Gross location	
Cortical	37 (17.1)
Subcortical	179 (82.9)
Anatomic location	
Frontal	56 (25.9)
Parietal	32 (14.8)
Temporal	4 (1.8)
Occipital	6 (2.7)
Basal ganglia	66 (30.6)
External/extreme capsule	23 (10.6)
Internal capsule	9 (4.2)
Cerebellum	18 (8.3)
Brainstem	2 (0.9)

158 of 892 subjects = 17%

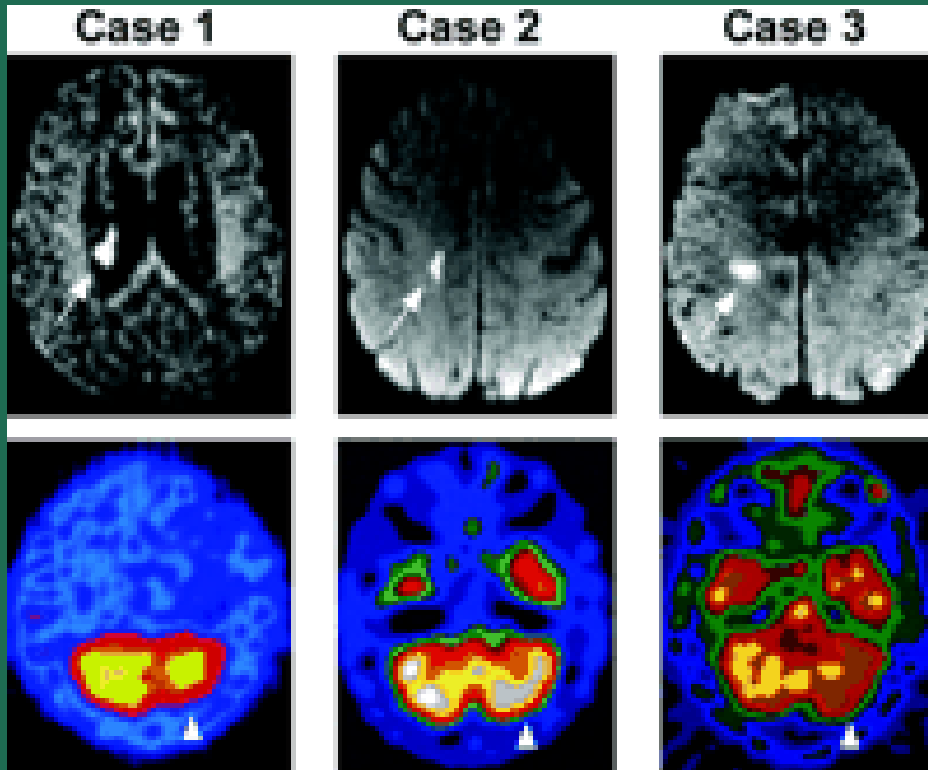
# SBI and Stroke Risk



SBI	Any Stroke			ISC Stroke		
	No. of event	Crude rate (/1000 PYS)	HR (95% CI)*	No. of event	Crude rate (/1000 PYS)	HR (95% CI)*
No (n=1043)	49	6.1	Ref.	42	5.3	Ref.
Subcortical (n=88)	7	10.7	1.31 (0.58-2.96)	6	9.1	1.34 (0.56-3.22)
Cortical (n=104)	15	20.5	2.50 (1.36-4.59)	15	20.5	2.98 (1.59-5.58)

\* adjusted for age, sex, race-ethnicity, education, medical insurance status, BMI, smoking, physical activity, moderate alcohol drinking, hypertension, diabetes, hypercholesterolemia, history of AF, CAD, and MI.

# Subclinical Infarction and Diaschesis

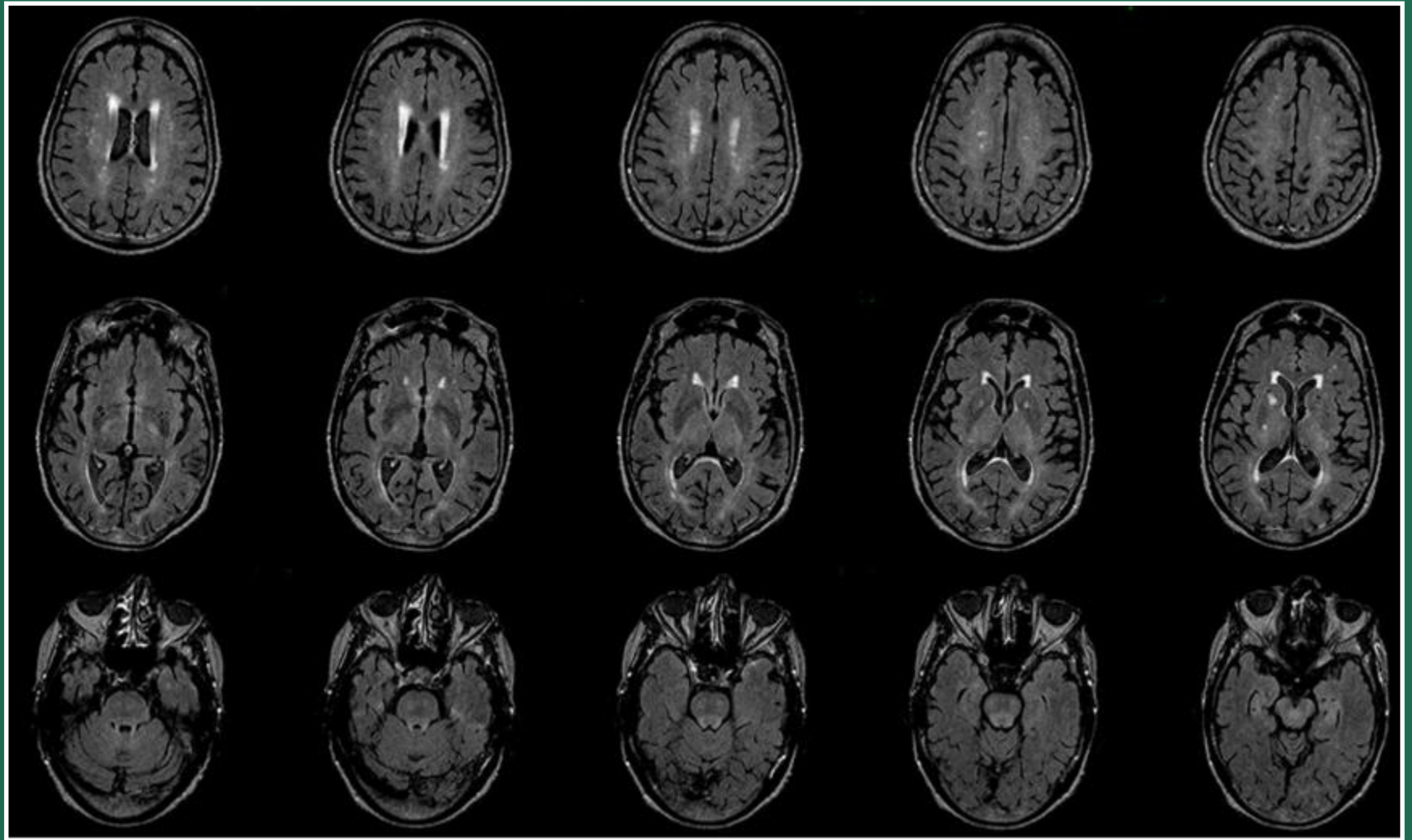


Infarcts in NOMAS associated with:

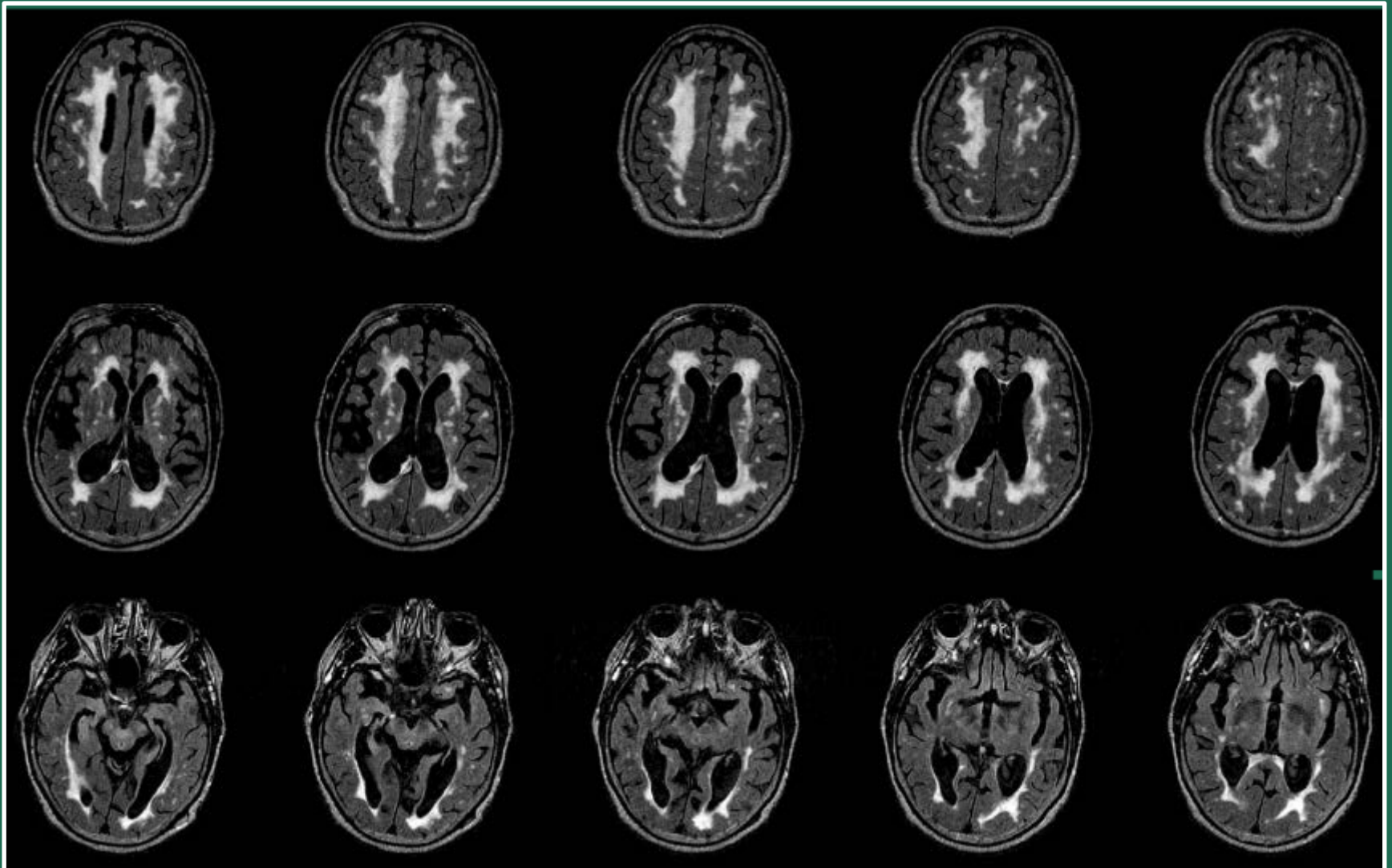
- Speed
- Cognitive flexibility
- Immediate verbal memory
- Delayed verbal memory

Stroke. 2006;37:e1

# White Matter Hyperintensity Volume = ~10%



# White Matter Hyperintensity Volume = ~90%



# Blood pressure and log-WMHV/TCV%

N=1281, Mean time between baseline and MRI=7.2 ± 2.4 years

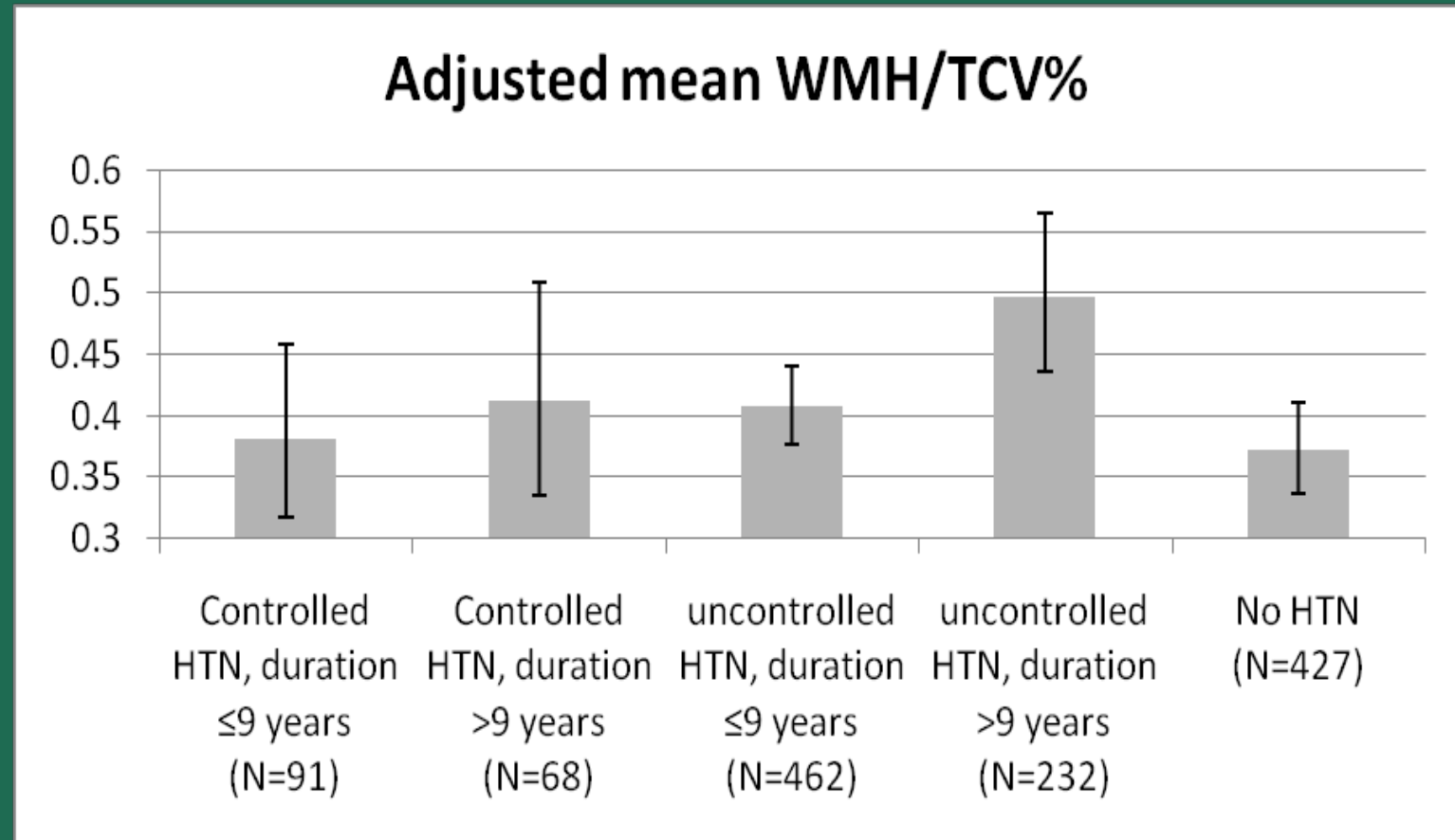
Measure of BP	Model 1 β (p value)	Model 2 β (p value)	Model 3 β (p value)
SBP*	0.02 (0.37)	0.02 (0.57)	-0.01 (0.78)
DBP*	<b>0.15 (&lt;0.0001)</b>	<b>0.15 (&lt;0.0001)</b>	<b>0.16 (&lt;0.0001)</b>
SBP increase <sup>†</sup>	-0.04 (0.61)	-0.05 (0.51)	-0.08 (0.29)
SBP decrease <sup>†</sup>	-0.03 (0.71)	-0.01 (0.90)	-0.03 (0.62)
DBP increase <sup>†</sup>	<b>0.22 (0.008)</b>	<b>0.20 (0.013)</b>	<b>0.19 (0.02)</b>
DBP decrease <sup>†</sup>	-0.05 (0.41)	-0.05 (0.43)	-0.07 (0.26)

Model 1: adjusted for age

Model 2: plus sex, race/ethnicity

Model 3: plus DM, LDL, HDL, smoking, ETOH use, HTN meds

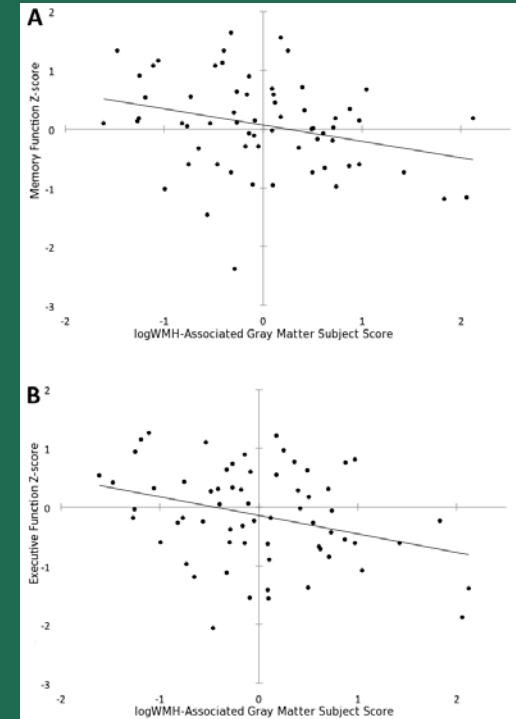
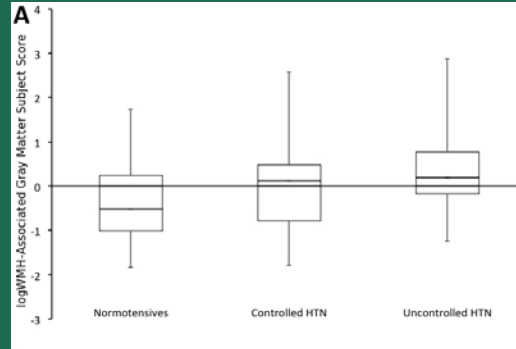
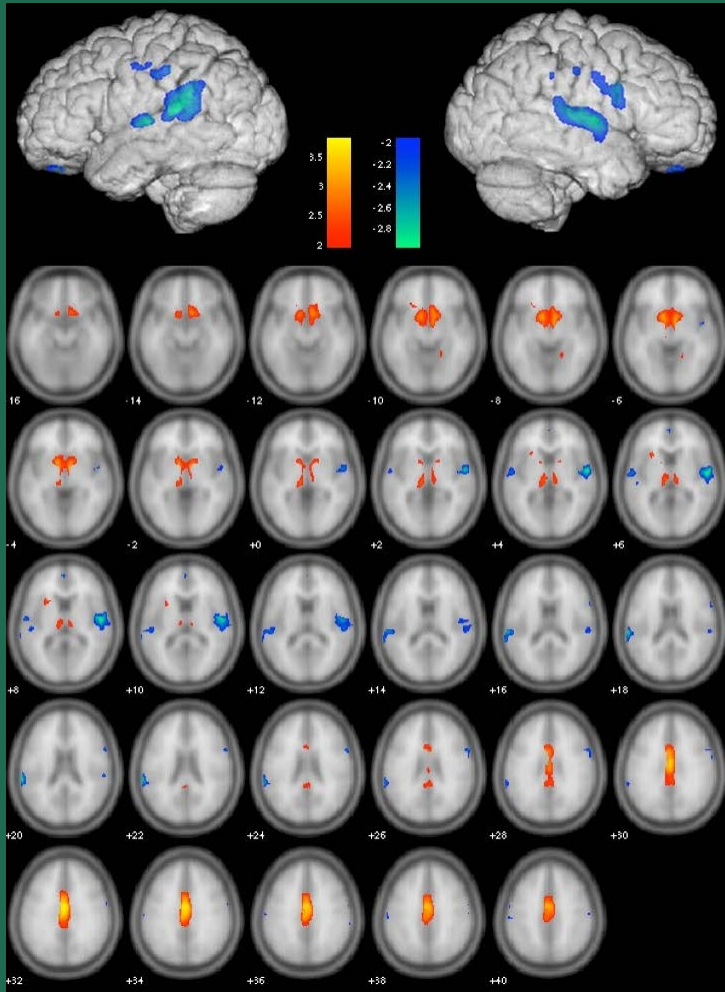
# Adjusted mean WMHV/TCV% by duration and control of hypertension reported at baseline



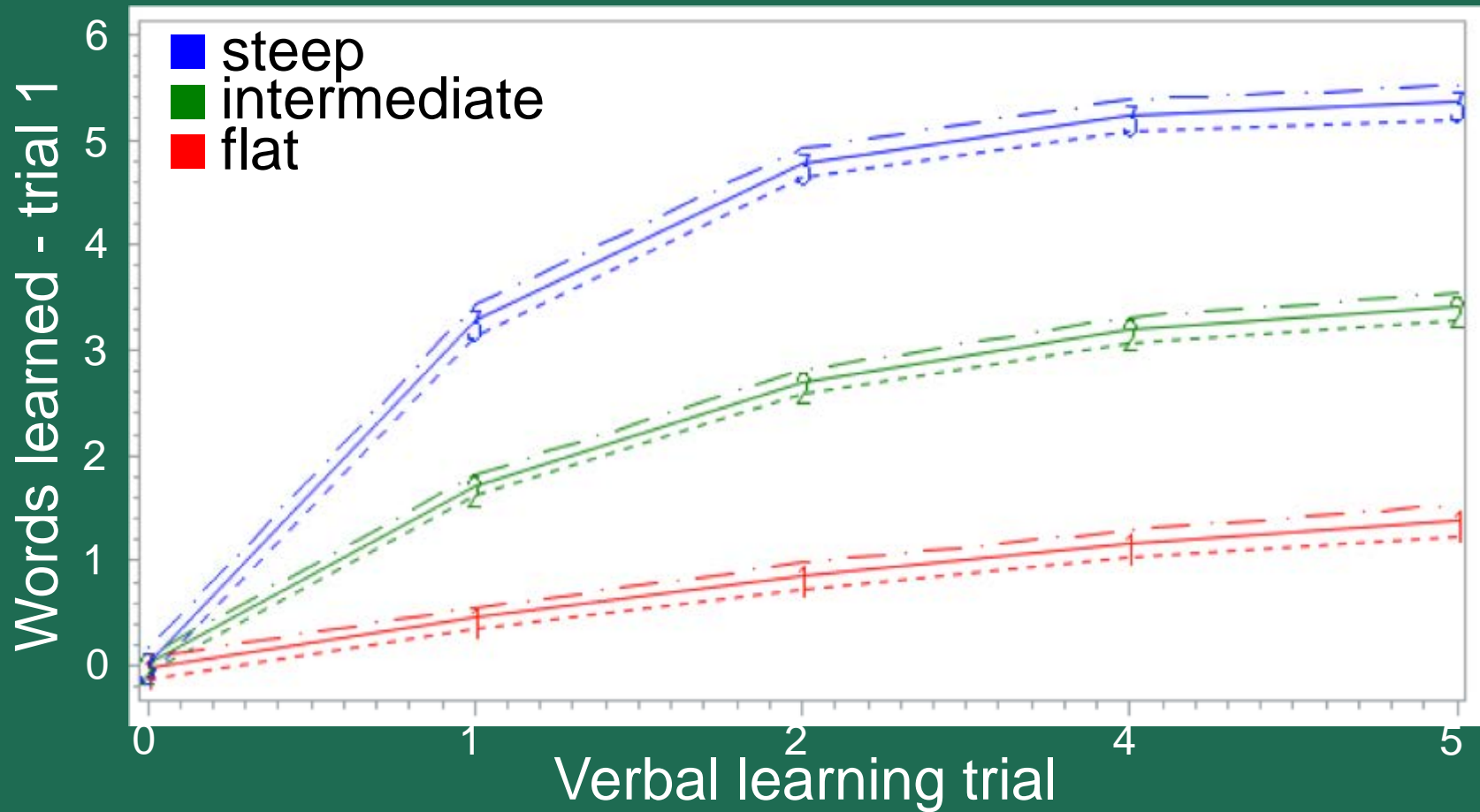
# Case control study of hypertension and WMH-related BV differences

	Total	Normotensives	Controlled Hypertensives	Uncontrolled Hypertensives	P values <sup>a</sup>
<b>N</b>	64	21	22	21	
<b>Age</b>	72 ± 7	72 ± 7	71 ± 8	71 ± 7	0.80
<b>Males:Female</b>	21:43	7:14	7:15	7:14	0.99
<b># with &lt; 8th grade Education</b>	35	12	12	11	0.95
<b>IQ Z-score</b>	0.08 ± 0.81	0.13 ± 0.97	0.06 ± 0.80	0.06 ± 0.68	0.95
<b>Memory Z-score</b>	0.07 ± 0.79	0.03 ± 0.88	0.15 ± 0.75	0.03 ± 0.73	0.85
<b>Executive Function Z-score</b>	- 0.14 ± 0.81	- 0.12 ± 0.84	- 0.07 ± 0.80	- 0.24 ± 0.81	0.80
<b>Processing Speed Z-score</b>	0.01 ± 0.35	- 0.03 ± 0.30	0.07 ± 0.40	- 0.02 ± 0.34	0.54
<b>Language Z-score</b>	0.01 ± 0.75	0.15 ± 0.89	- 0.01 ± 0.69	- 0.11 ± 0.67	0.54
<b>Total Cerebral Volume (cc)</b>	1138 ± 118	1137 ± 99	1130 ± 118	1146 ± 139	0.91
<b>WMH Volume</b>	7.7 ± 9.1	5.6 ± 7.7	9.0 ± 8.3	8.4 ± 11.1	0.45
<b>WMH Brain Volume %<sup>b</sup></b>	0.66 ± 0.73 %	0.48 ± 0.61 %	0.78 ± 0.70 %	0.70 ± 0.85 %	0.38

# Case control study of hypertension and WMH-related BV differences



# Verbal learning trajectories



# SCVD and slope of verbal learning

	<b>Slow vs. Fast</b>	<b>Medium vs. Fast</b>
	<b>OR (95% CI)</b>	<b>OR (95% CI)</b>
<b><u>Model 1</u></b>		
<b>Subclinical infarcts</b>	2.19 (1.06, 4.54)	1.93 (1.01, 3.69)
<b>Total brain volume</b>	0.95 (0.90, 1.01)	1.00 (0.95, 1.04)
<b><u>Model 2</u></b>		
<b>White matter hyperintensity volume</b>	1.71 (1.27, 2.30)	1.53 (1.16, 2.01)
<b>Total brain volume</b>	0.94 (0.89, 1.00)	0.99 (0.94, 1.03)
<b><u>Model 3</u></b>		
<b>Subclinical infarcts</b>	1.59 (0.75, 3.38)	1.52 (0.78, 2.96)
<b>White matter hyperintensity volume</b>	1.62 (1.18, 2.22)	1.46 (1.09, 1.95)
<b>Total brain volume</b>	0.95 (0.90, 1.01)	1.00 (0.95, 1.04)

Adjusted for age, education, sex, race-ethnicity, and medical insurance status.

# Legend for Lobar Regional Volume

14 volume measurements for each subject is provided

**Deep WMH**  
(distance to ventricle >10mm)

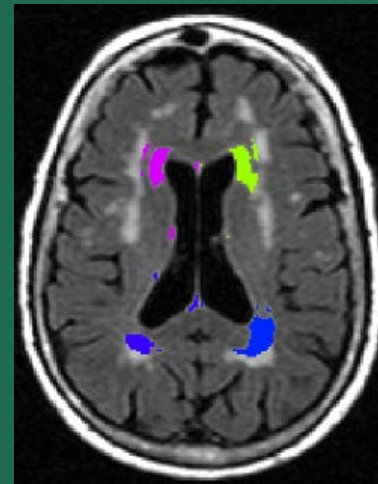
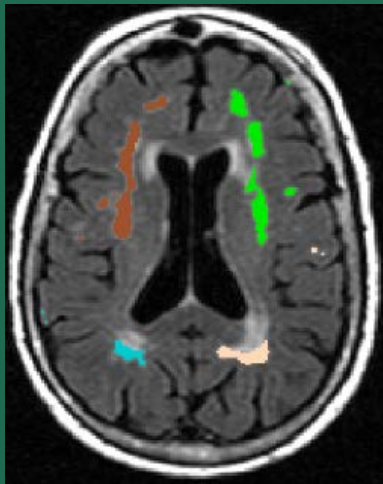
10 regions are labeled as  
lh\_FL, rh\_FL, lh\_PL, rh\_PL, lh\_OL, rh\_OL,  
lh\_TL, rh\_TL, CRB, BS

\*4 cerebellar lobes (FL, PL, OL, TL) in 2  
hemispheres (lh/rh)  
cerebellum and brain stem (CRB,BS)

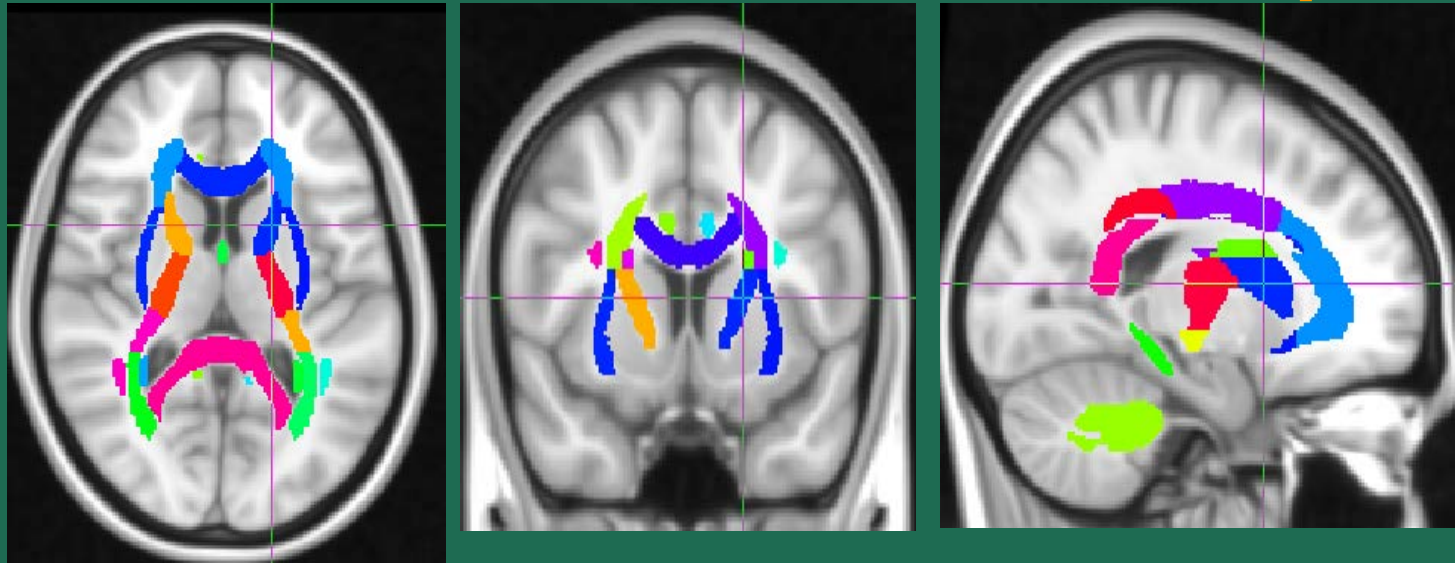
**Periventricular WMH**  
(distance to ventricle <10mm)

4 regions are labeled as

lh\_aWM: Left hemisphere anterior WMH  
rh\_aWM: Right hemisphere anterior WMH  
lh\_pWM: Left hemisphere posterior WMH  
lh\_pWM: Right hemisphere posterior WMH



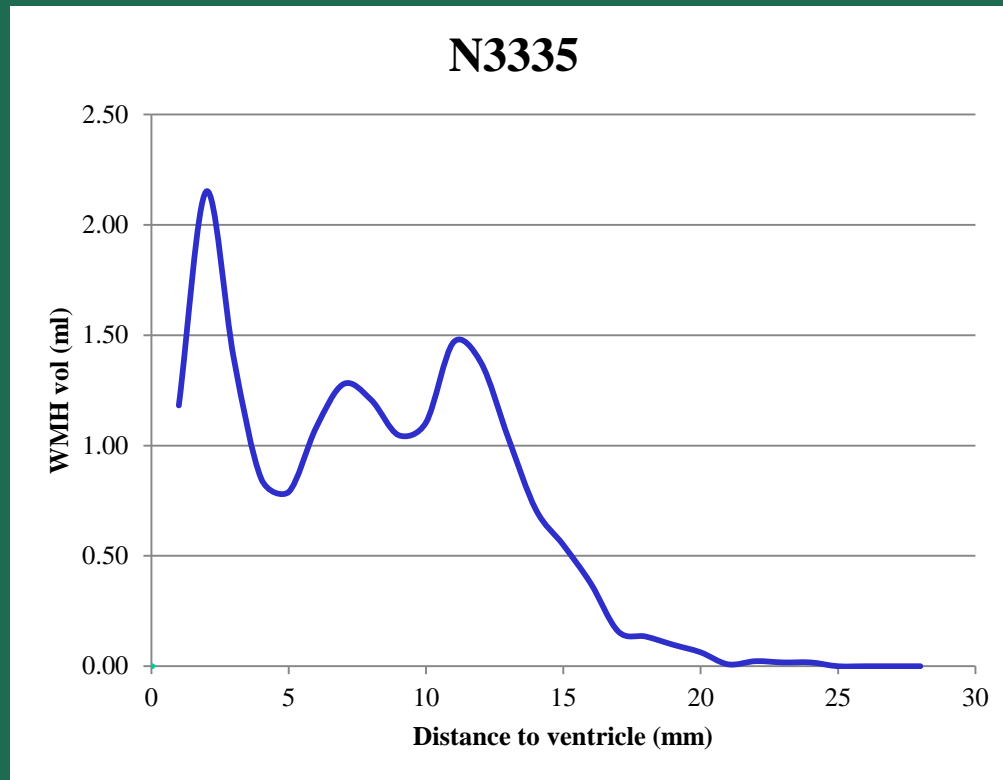
# JHU DTI-based WM atlas description



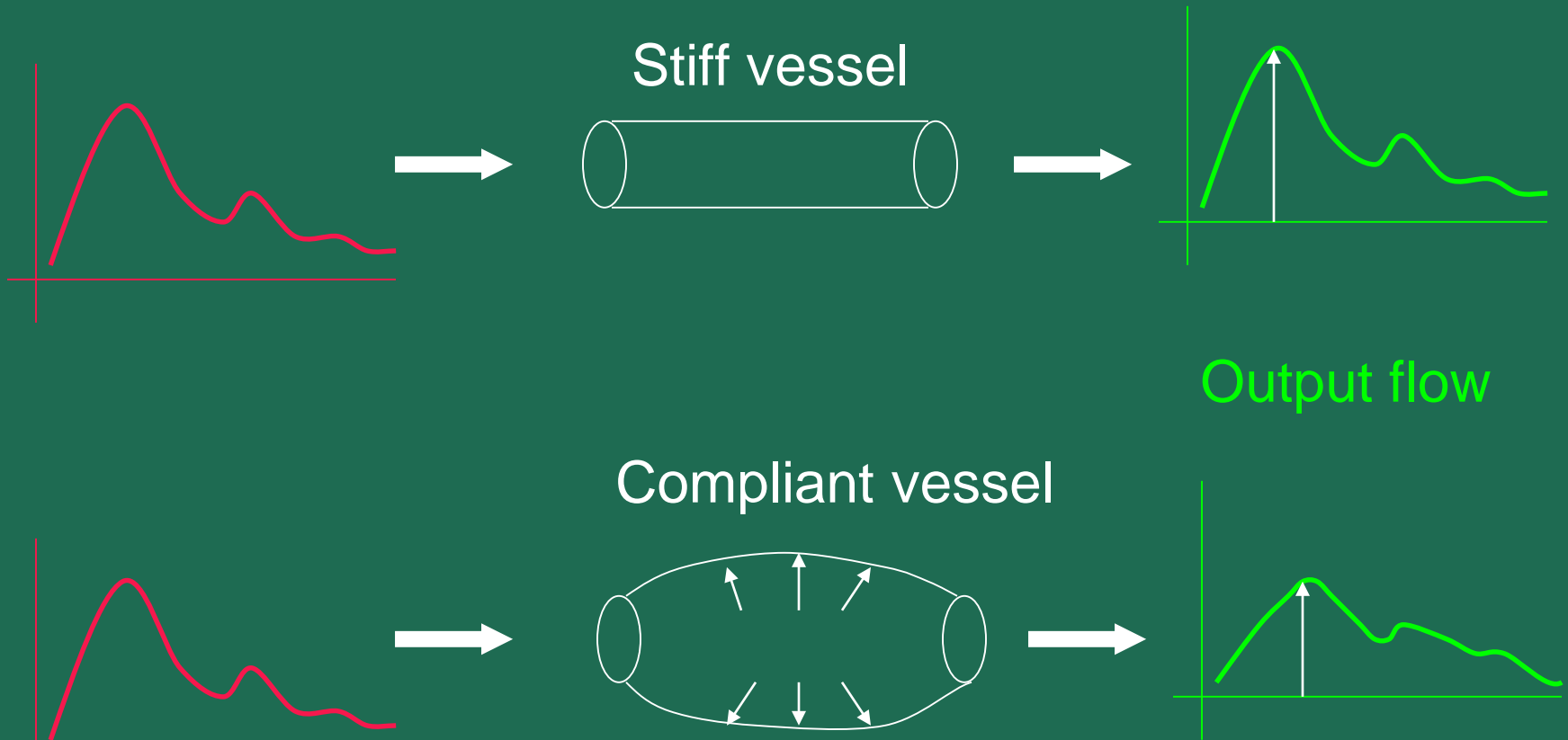
- The atlas is provided with FSL software package with the following description:
- ICBM-DTI-81 white-matter labels atlas:
  - 48 white matter tract labels were created by hand segmentation of a standard-space average of diffusion MRI tensor maps
  - from 81 subjects; mean age 39 (18:59), M:42, F: 39.
  - The diffusion data was provided by the ICBM DTI workgroup.

# Distance Maps

Volume of WMH as a function of distance from the ventricle wall

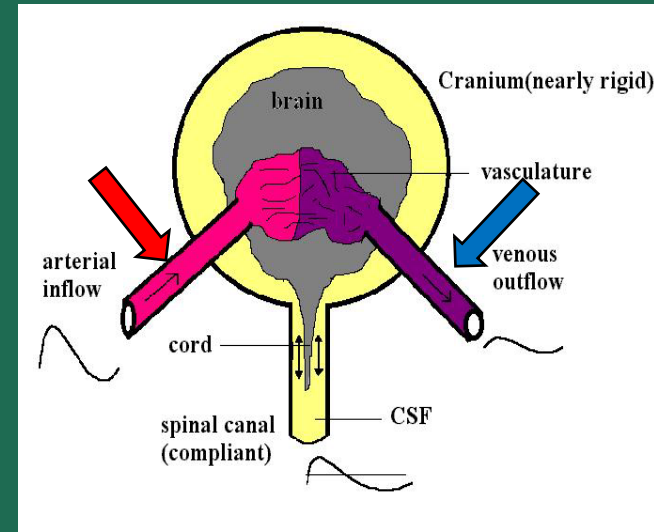


# Effect of Stiffness on Flow Dynamics

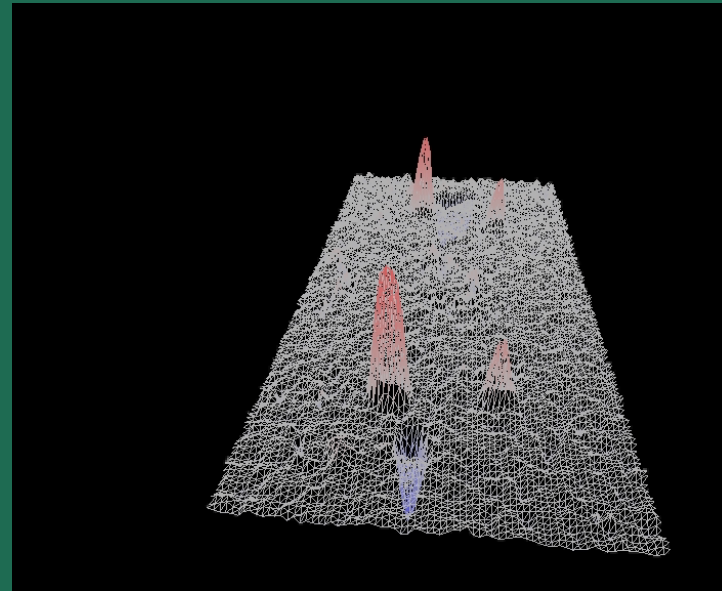
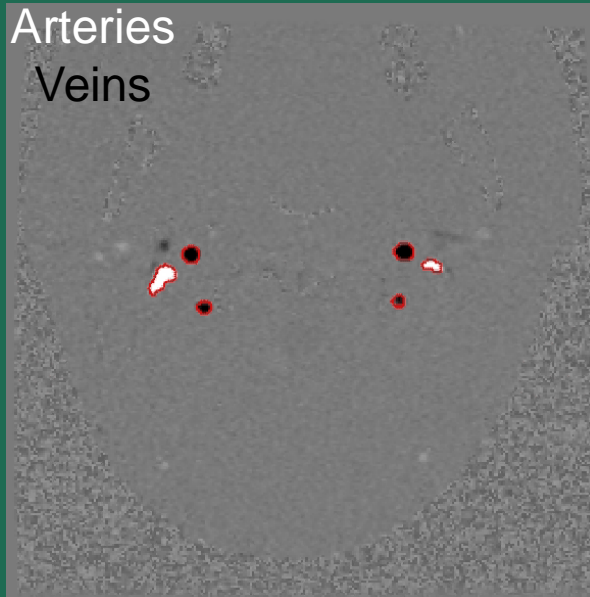


Measurements of vascular expansion require both the input and output flow rates

# MRI measurement of Cerebral Blood Flow



Arteries  
Veins



# Pulsatility Measures vs. Regional Brain Volumes

## Subjects:

UM memory clinic.

Total: 66 (43 women)

Age:  $72 \pm 9.3$  (49 - 88)

## Pulsatility Measures:

Arterial Pulsatility index

Arterial expansion

Venous pulsatility index

Venous expansion

A-V (vascular) expansion

## Volumetric Measures (partial list)

Frontal, parietal, temporal, occipital

Hippocampus

Cerebral WM

Ventricular volume

MMSE Score	Cognitive Impair.	Number of Subjects
0 - 9	Severe	2
10 - 18	Moderate	10
19 - 24	Mild	17
24 <	bor. normal	35

Total cerebral blood flow (tCBF)  
positively associated with:

- Total brain tissue (beta=278, p=0.03)
- Global cognition (MMSE) (beta=0.686, p=0.003)

# Future Directions

- Focused enrollment of participants 85+ years of age
- Characterize the sample
- Build in MRI techniques that capture vascular changes
- Select and develop cognitive tests most suitable to studying cognitive aging in the oldest old
- Develop collaborative programs that include other MBI resources and strengths

# UM MBI Members and Collaborators

N Alperin

A Bagci

B Baumel

S Blanton

Y Campos

C Cohan

E Crocco

S Czaja

M Diaz

K Dave

C Dong

H Gardener

J Gomes-Osman

H Jiang

B Levin

K Lin

M Mendoza-Puccini

T Monteith

C Moraes

N Nabizadeh

J Neumann

M Perez-Pinzon

A Ramos

A Raval

T Rundek

R Sacco (Executive Director)

X Sun (Education Director)

C Wright

J Young

A Zeki Al Hazzouri

# Next steps

- Frontiers special edition: Neuroimaging and cognitive aging
- Augmenting Cognitive Training (ACT) grant (impact score 16)
- Continue development of Brain Aging Registry in oldest old
- Analysis of inter-relationships between multimodal

Big picture agenda: Understanding successful aging

- Biomarker development
- Normative imaging and cognitive measures in the oldest old
- Clinical interventions for cognitive aging based on above discoveries