Greater Aortic Stiffness is Associated with Lower Hippocampal Cerebrovascular Reserve but not Cerebral Blood Flow in Middle-aged and Older Adults

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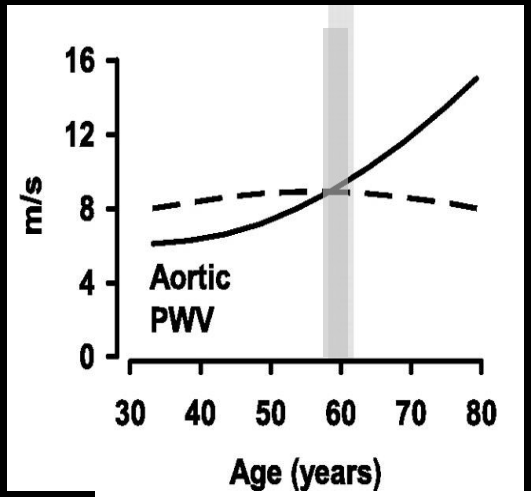
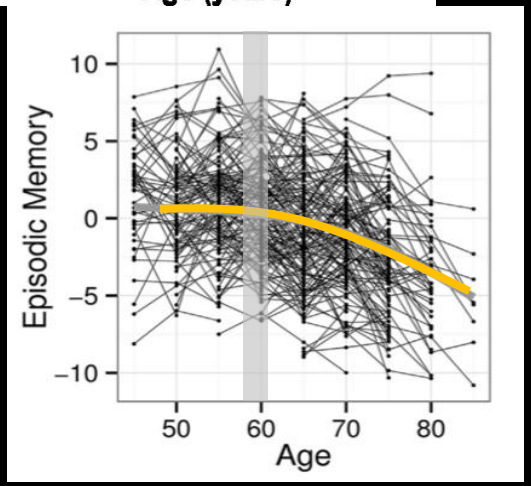
Arterial stiffness and the aging brain

- Mild cognitive impairment (MCI) is a transitional stage between normal aging and dementia.
  - Amnestic MCI is defined by declines in memory performance only that are greater than age- expected declines.
  - Thirty percent (30%) of individuals with MCI have amnestic MCI. (Peterson et al., J Intern Med, 2004)
  - Approximately 12% of individuals with amnesic MCI will progress to Alzheimer's disease within 1 year. (Peterson et al., J Intern Med, 2004)

Arterial stiffness and the aging brain

- Aortic stiffness is a risk factor for the development of MCI. (Pase et al., Stroke, 2016)
  - Aortic stiffness mediates age-related reductions in memory performance. (Cooper et al., Stroke, 2016)
- Hippocampal dysfunction is implicated in the development of amnesic MCI. (Huijbers et al., Brain, 2015; Tran et al., NeuroImag, 2017)
  - Altered hippocampal neuronal activation (BOLD fMRI) (Huijbers et al., 2015)
  - Aortic stiffness is associated with reductions in <u>global</u> cerebrovascular reserve (CVR) and increased amyloid deposition. (DuBose et al., Hypertension, 2018; Hughes et al., Neurology 2018)





Mitchell, JAP, 2008
Gorbach et al., Neurobiology of Aging, 2016

The degree to which aortic stiffness
is associated with functional hippocampal cerebral blood flow (CBF) impairments during memory stimulation,
CVR or amyloid deposition is unknown.

Primary hypothesis:

Elevated aortic stiffness would be associated with lower hippocampal CBF during memory stimulation and reduced hippocampal CVR.

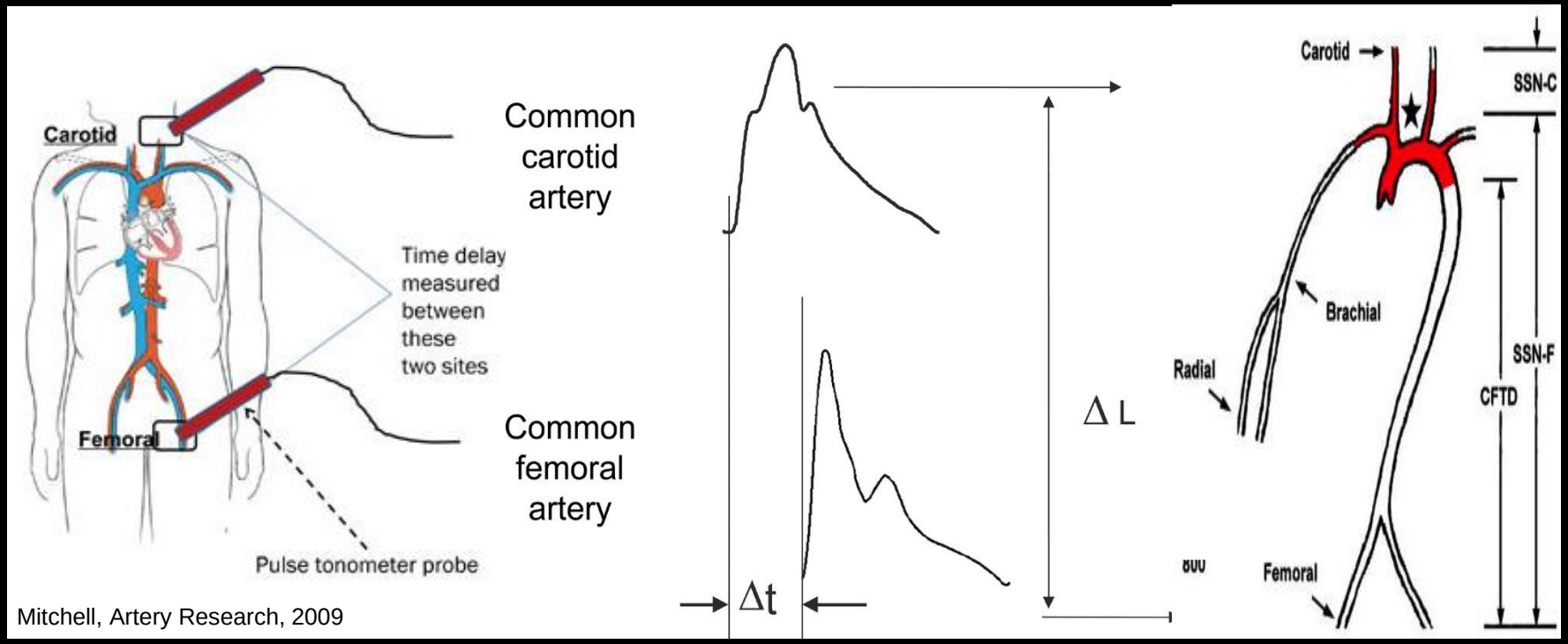
Secondary hypothesis:

Greater aortic stiffness would be associated with elevated hippocampal amyloid burden.

Cross-sectional Study

- Adults aged 55-87 years (n=24) were recruited from the Iowa City, IA, USA community to complete vascular testing and PET imaging.
- Two individuals had mild cognitive impairment (MCI) according to Alzheimer's Disease Neuroimaging Initiative (ADNI-II) criterion
- **Vascular altering medication was held on the morning of vascular testing.**

Clinical Measurement of Aortic Stiffness



Mitchell, Artery Research, 2009

Carotid-femoral pulse wave velocity (CF-PWV)

ΔL= (carotid-femoral distance)- (SSN to carotid distance)

PWV = ΔL /Δt

PET Imaging

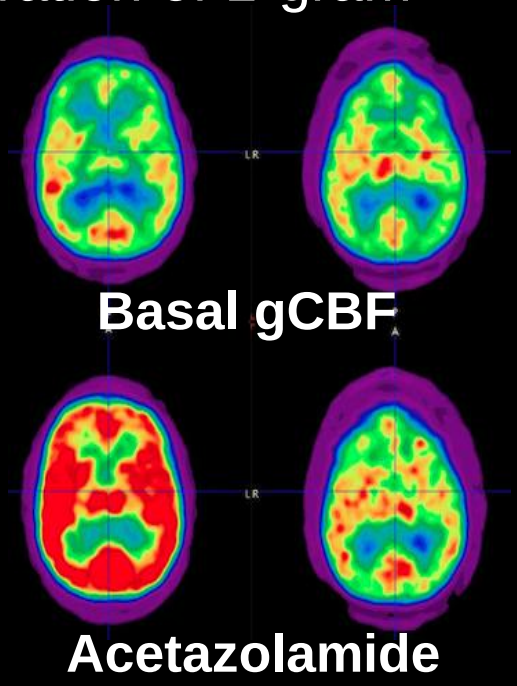
Assessment of hippocampal CBF:

- [^{15}O]water PET imaging is "gold-standard" for human CBF determinations
- *Quantitative* measure of CBF
- Hippocampal CBF was determined using the brain parcellation routine of PMOD Neuro Tool (Pneuro, PMOD Technologies) and T1 anatomical MRI image

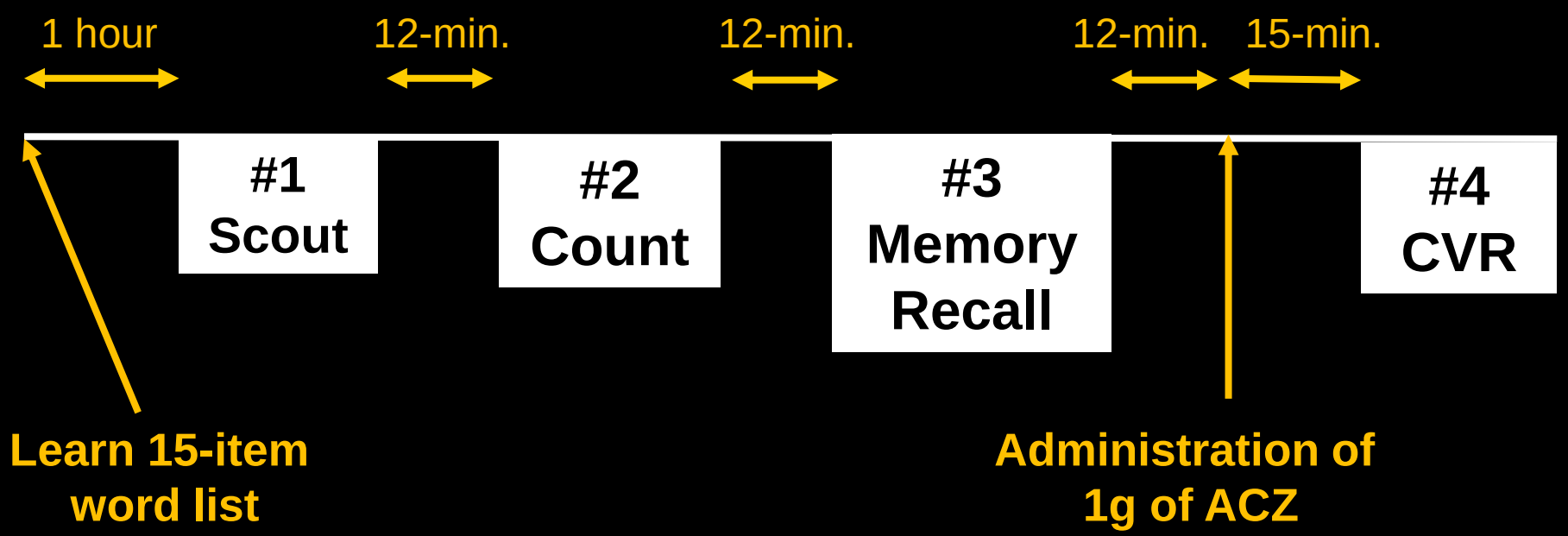
PET Imaging

- Assessment of hippocampal CVR:
  - Acetazolamide (ACZ) (Diamox®), a carbonic anhydrase inhibitor
  - Image collected 15 minutes post IV administration of 1-gram ACZ bolus
  - "Gold-standard" measure of CVR

$$CVR(\%) = \frac{[(\text{ACZ blood flow} - \text{basal CBF})]}{\text{basal CBF}} \times 100$$

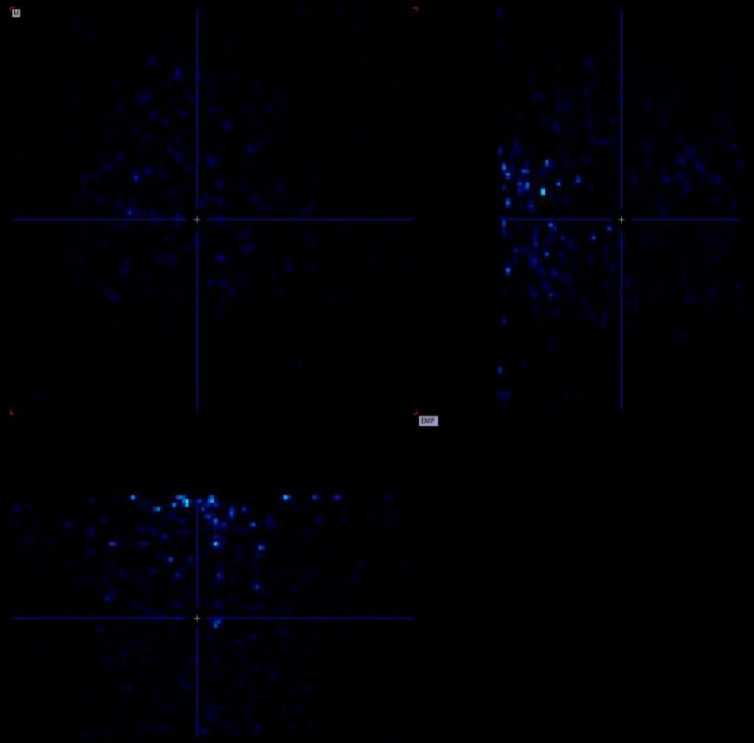


PET Imaging


1 hour
12-min.
12-min.
12-min.
15-min.
#1 Scout
#2 Count
#3 Memory Recall
#4 CVR
Learn 15-item word list
Administration of 1g of ACZ

PET Imaging

- Uptake of [^{11}C] Pittsburgh Compound B (PiB) is an index of β-amyloid plaque burden
- Dynamic images (90 minutes, wash-in/wash-out) were analyzed to calculate distribution volume ratios (DVR)
- Values >1 indicate amyloid deposition; >1.5 indicate clinically positive test
- Regions were defined on the individual's structural T1-weighted MRI



Results

Subject Characteristics:	Mean ± SE N=24
Age (years)	70 ± 2
Males/Females	16/8
Education (years)	16 ± 0.5
BMI (kg/m^2)	27 ± 1
Mild Cognitive Impairment, n (%)	2 (8)

Participants tended to be older, highly education and cognitively normal as defined by clinical criterion.

Results

Subject Characteristics:	Mean ± SE N=24
Baseline Blood Pressure	
Brachial systolic BP (mmHg)	119 ± 3
Brachial diastolic BP (mmHg)	64 ± 1
Brachial PP (mmHg)	55 ± 3
Aortic stiffness:	
cfPWV (m/sec)	10.1 ± 0.5

On average, participants were normotensive and within age-expected measures of cfPWV.

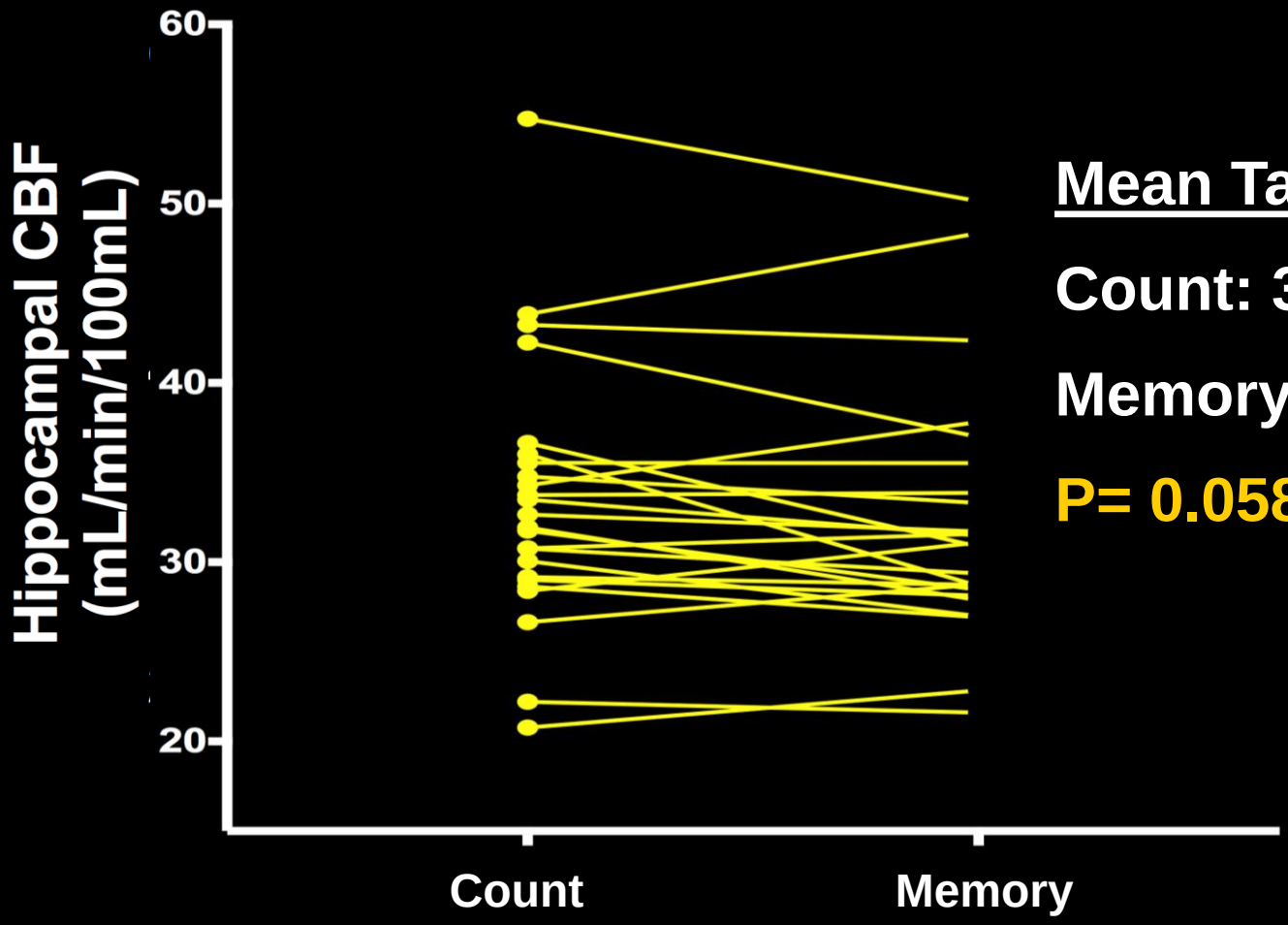
Results

Subject Characteristics:	Mean ± SE N=24
Baseline Blood Pressure	
Brachial systolic BP (mmHg)	119 ± 3
Brachial diastolic BP (mmHg)	64 ± 1
Brachial PP (mmHg)	55 ± 3
Aortic stiffness:	
cfPWV (m/sec)	10.1 ± 0.5

MAP was not altered with task stimulus (p= 0.105).

Results

Cerebral Blood Flow	Mean ± SE N=24
Global CBF (mL/min/100mL of tissue)	35 ± 1
Global CVR (%)	36 ± 4
Hippocampal CBF (mL/min/100 mL of tissue)	35 ± 2
Hippocampal CVR (%)	34 ± 4
Amyloid Burden	
Cortical PiB retention	1.3 ± 0.6
Amyloid-β (+) test, n (%)	5 (20)
Hippocampal PiB	1.3 ± 0.3
Memory Performance	
Memory recall (%)	64 ± 5.2



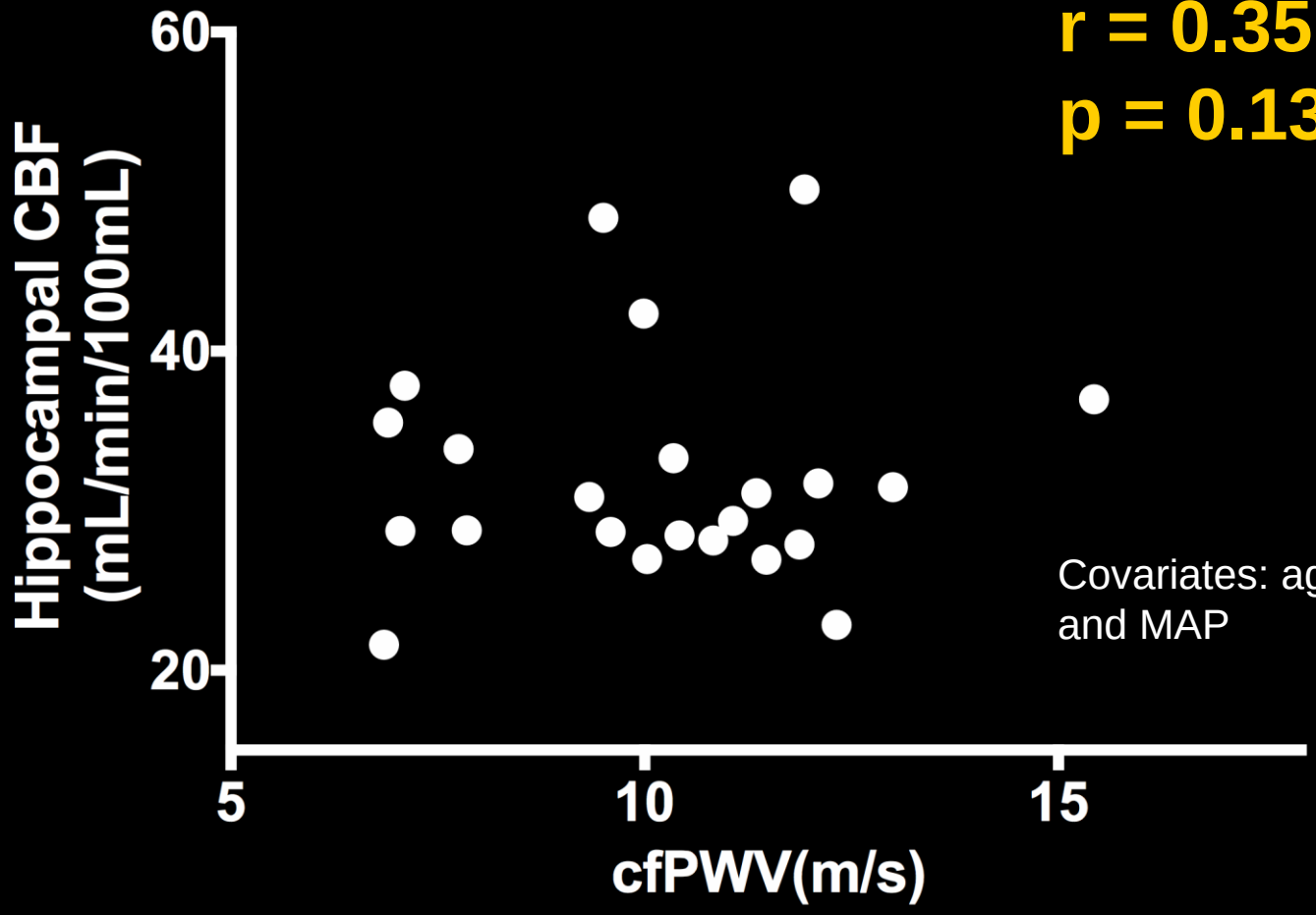
Mean Task CBF:

Count: 33.7 ± 1.4

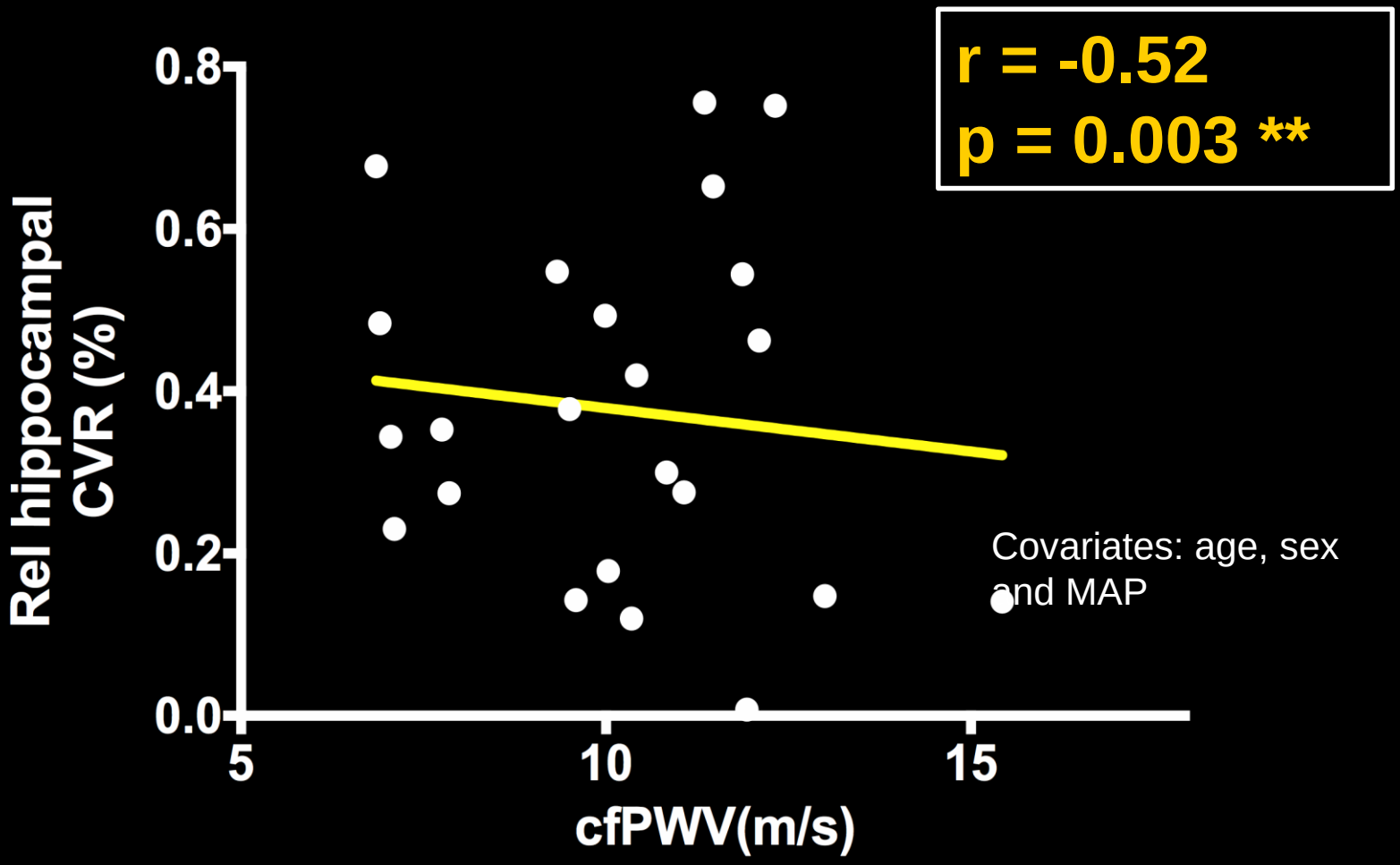
Memory: 32.5 ± 1.4

P= 0.058

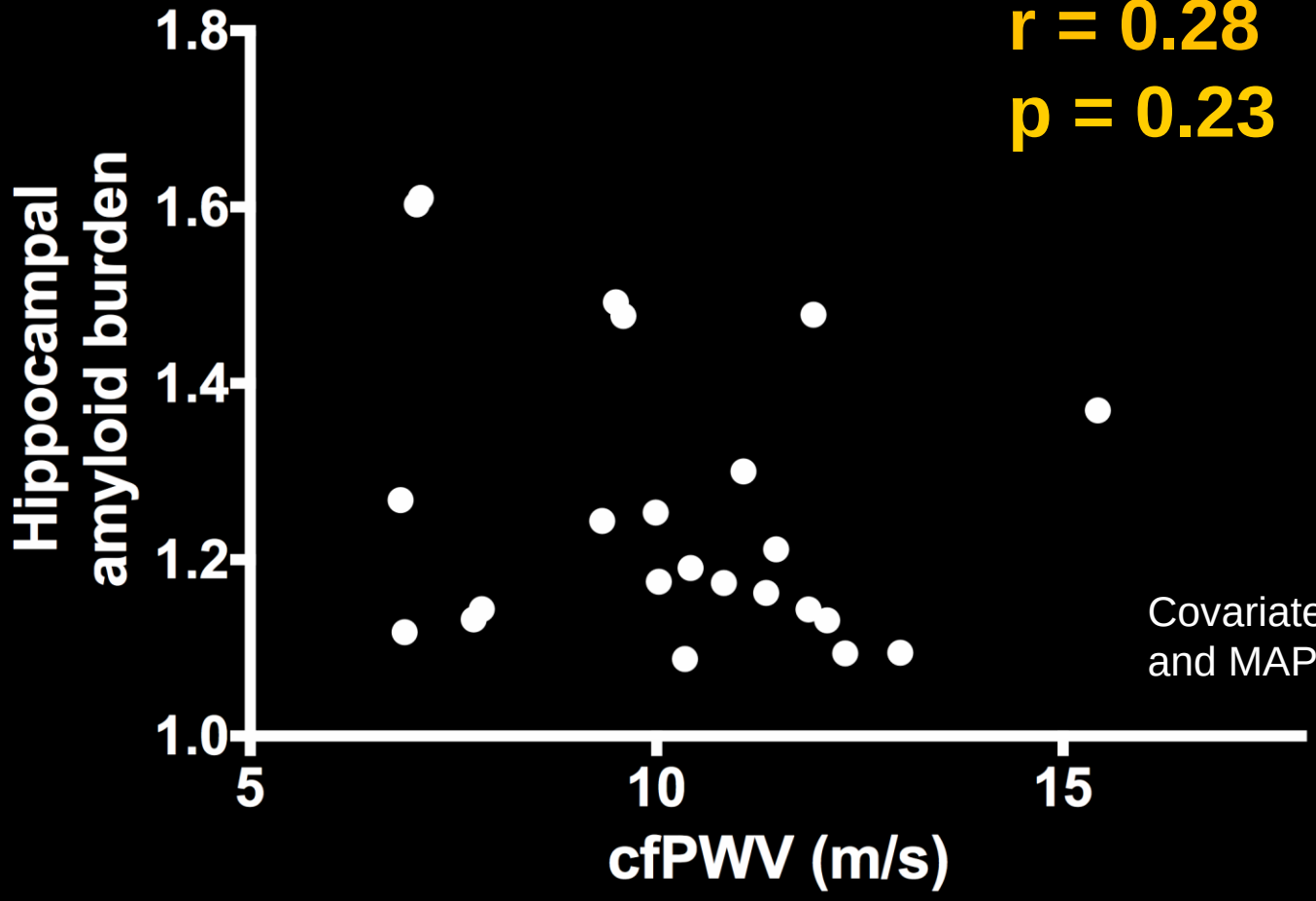
Hippocampal CBF did not significantly change in response to the memory task compared with baseline.



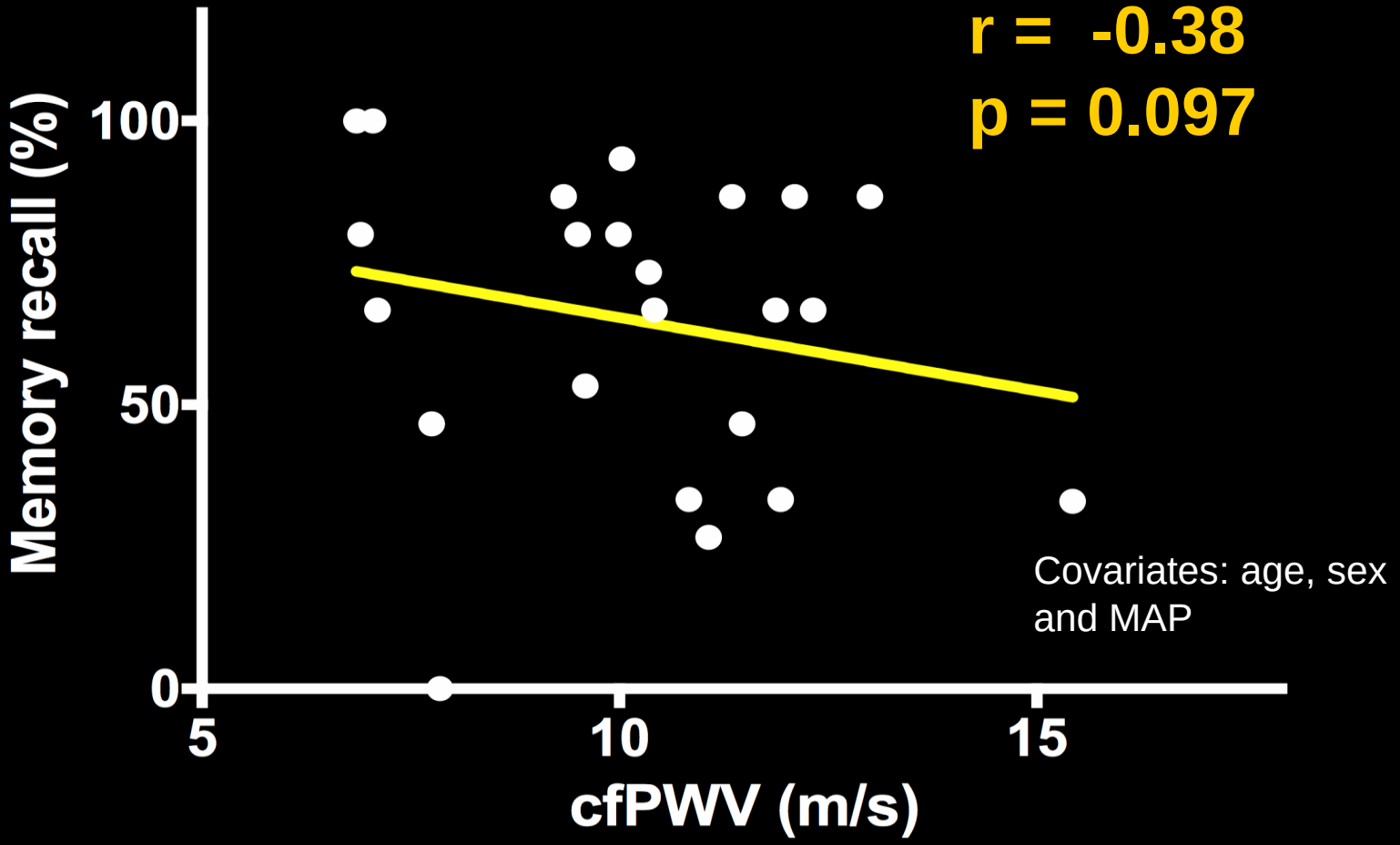
Aortic stiffness was not associated with hippocampal CBF during memory recall.



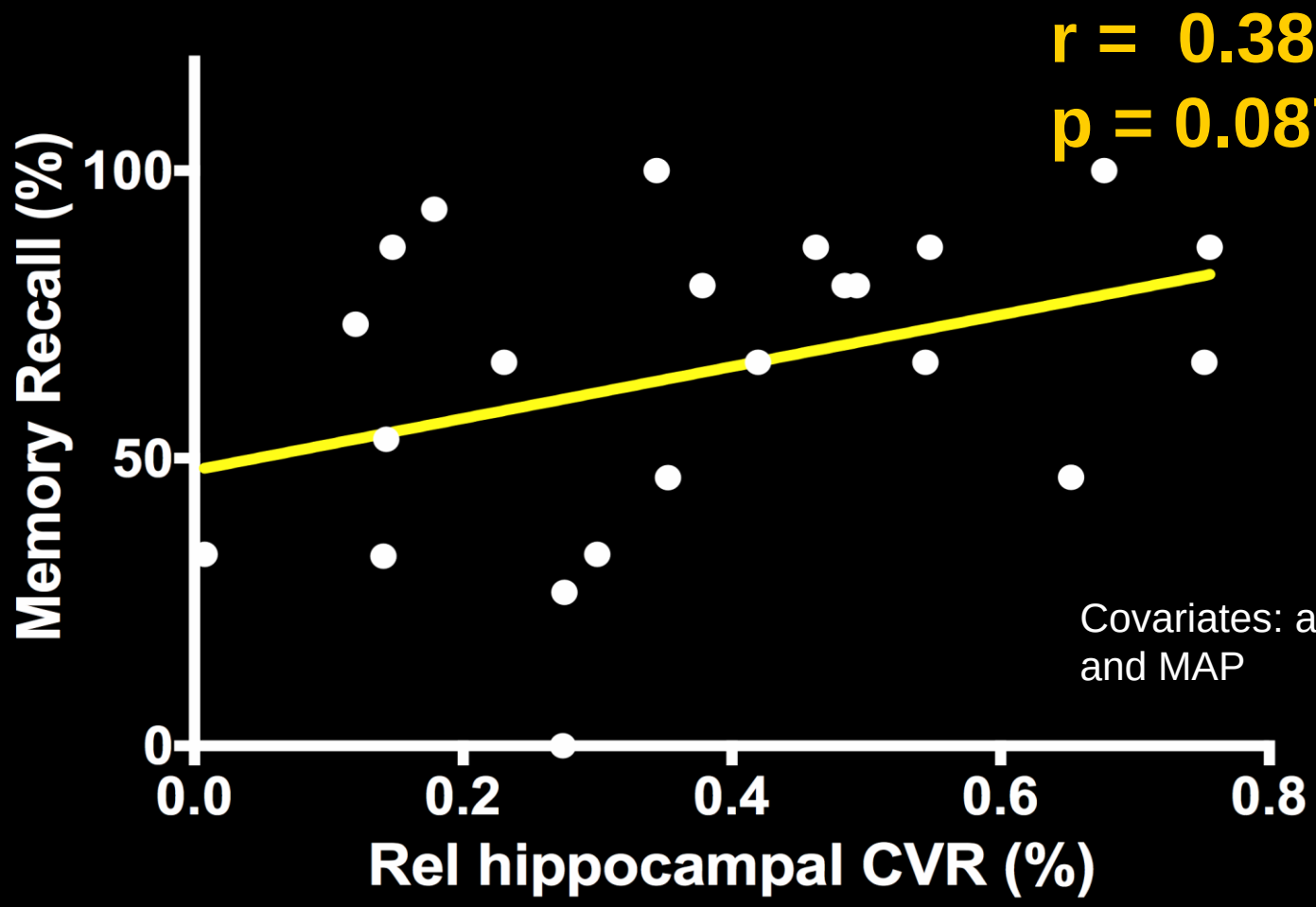
Elevated aortic stiffness was associated with reduced hippocampal CVR



Aortic stiffness was not associated with hippocampal amyloid deposition.



Aortic stiffness was not significantly correlated with lower percent word recall.



Hippocampal CVR was not significantly correlated with higher percent word recall.

Summary and conclusions

- Higher aortic stiffness was associated with reduced hippocampal CVR but not hippocampal CBF during the memory task.
  - Elevated aortic stiffness may impair the ability of the hippocampal cerebrovasculature to augment CBF.
  - Reductions in memory global CBF compared with the counting task is associated with lower learning performance in patients with MCI. (Ponto et al., 2006)
  - More studies are needed to understand if increased hippocampal activation compensates in part for reduced cerebrovascular function.

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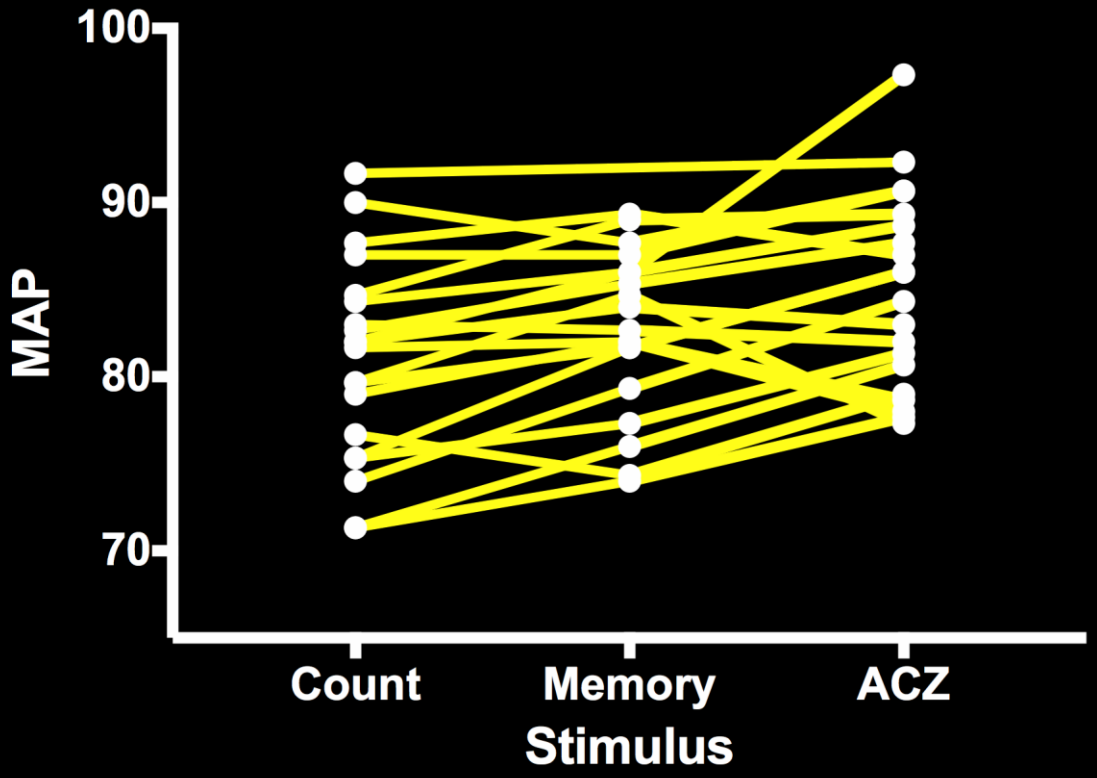
Supplemental

- Potential explains for the trend in hippocampal blood flow with memory stimulation:
    1. Subjects become anxious
    2. Other brain regions are being utilized
    3. Increased oxygen extraction (↑ deoxy BOLD signal) due to reduction in vascular dysfunction
    4. Sample size
    5. Difference in stimulus, neuroimaging technique

BP Response to Task



p=0.105

Supplemental

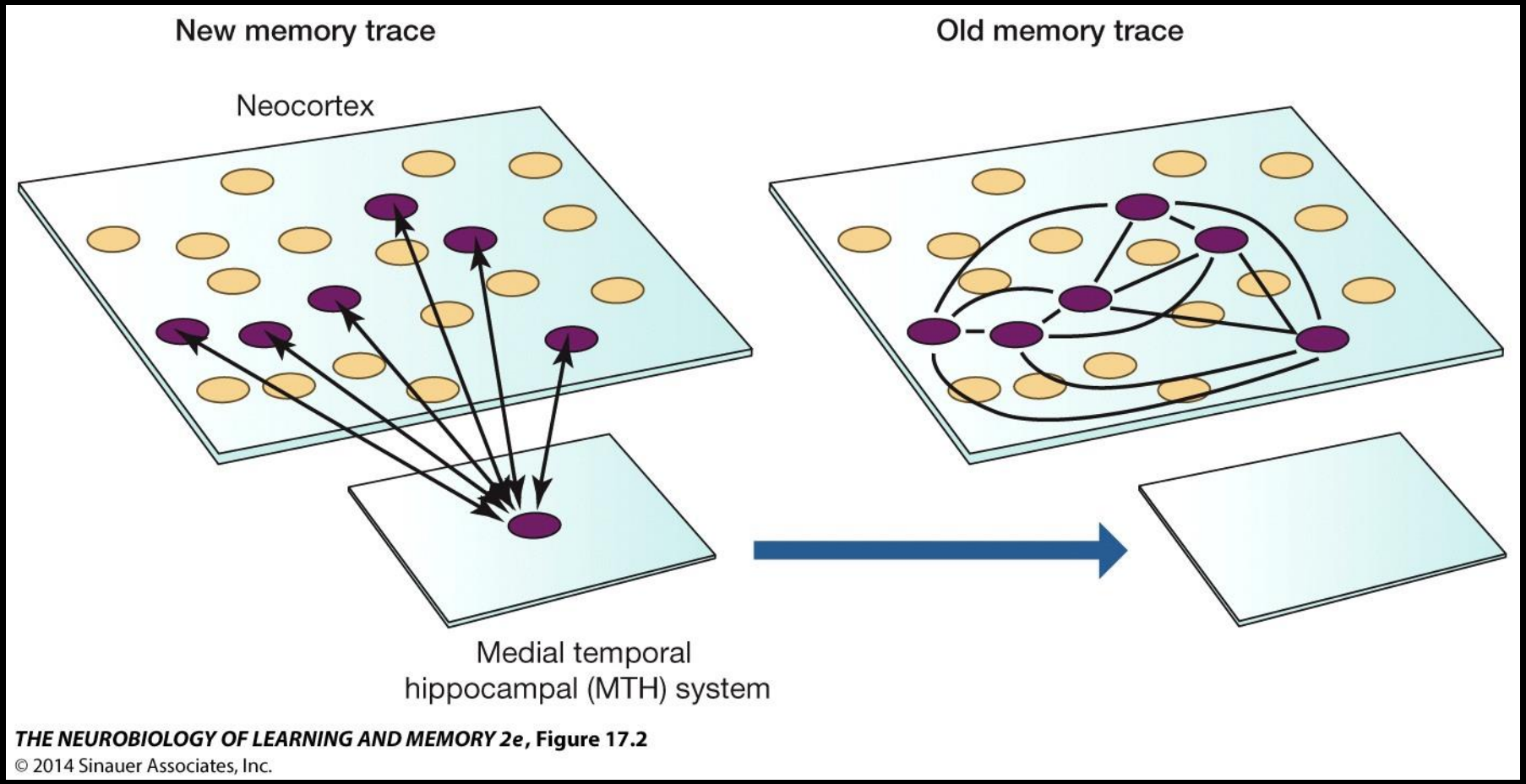
	Hippocampal CBF	Hippocampal CVR	Hippocampal PiB
Brachial SBP	0.19 (0.457)	-0.49 **(0.045)****	-0.43 (0.088)
Brachial DBP	0.20 (0.446)	-0.14 (0.581)	-0.520 **(0.032)****
Brachial PP	0.12 (0.659)	-0.44 (0.075)	-0.22 (0.397)

Covariates: age, sex

Supplemental

	Global basal CBF	Global CVR	Global PiB
Brachial SBP	0.01 (0.965)	-0.21 (0.443)	-0.01 (0.956)
Brachial DBP	0.29 (0.269)	-0.10 (0.720)	0.38 (0.131)
Brachial PP	-0.14 (0.587)	-0.15 (0.585)	-0.22 (0.397)

Covariates: age, sex



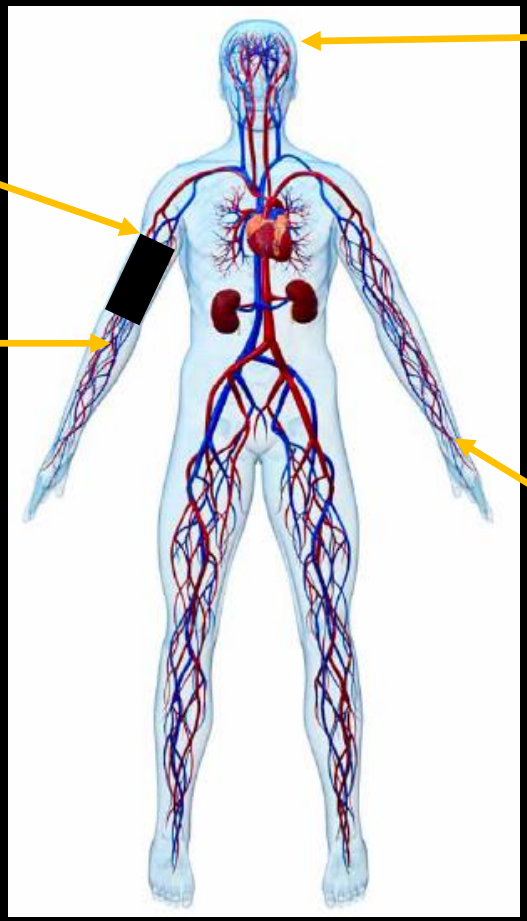
***THE NEUROBIOLOGY OF LEARNING AND MEMORY 2e*, Figure 17.2**

PET Imaging

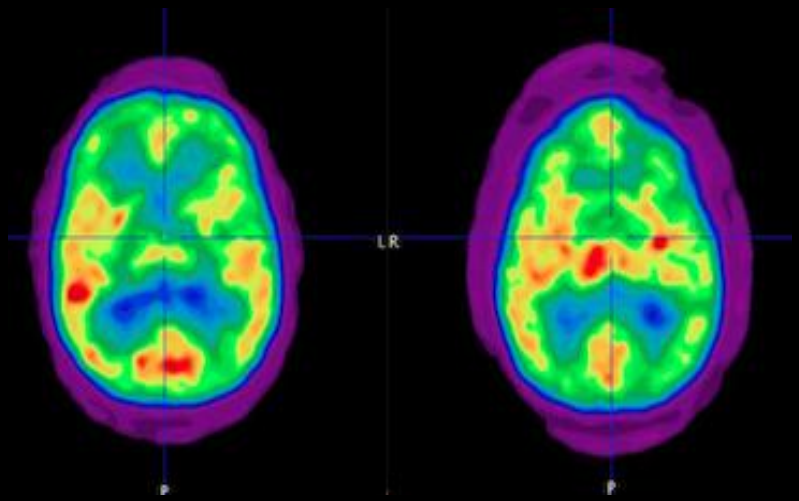
PET scanner

BP cuff

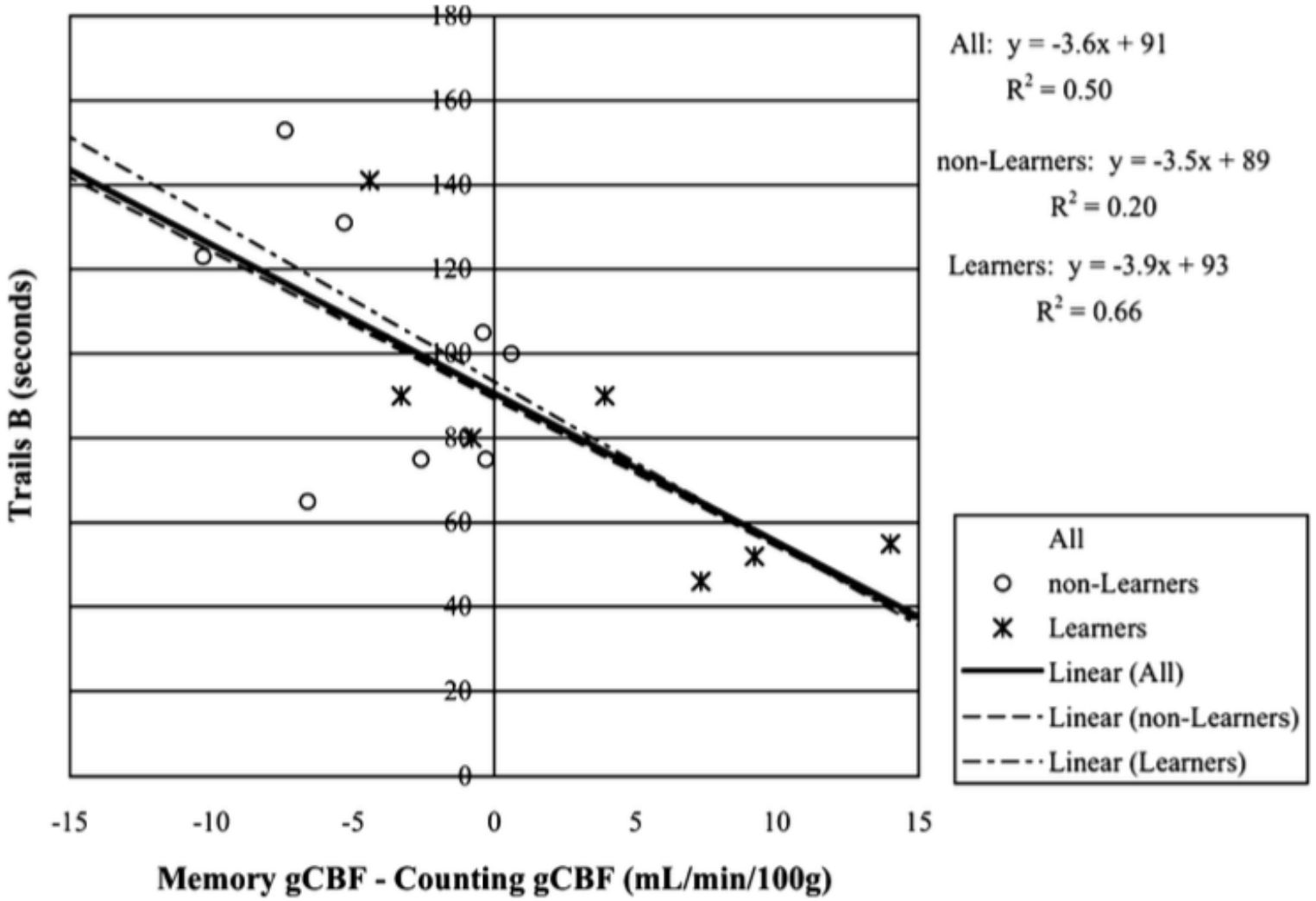
Venous catheter:
[^{15}O] water is injected



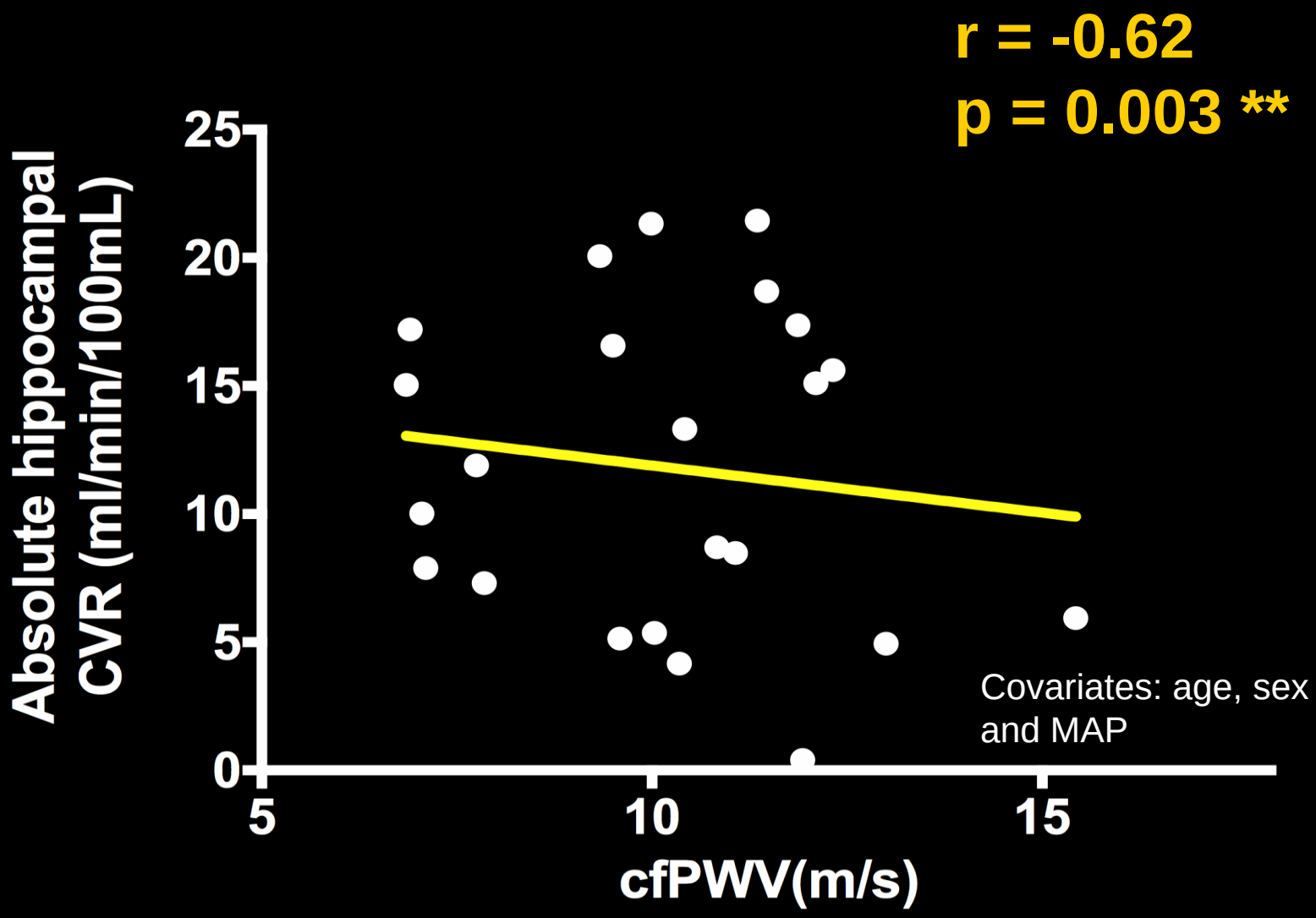
Radial arterial line:
[^{15}O] water is sampled



CBF images = arterial input function +
[^{15}O] water brain concentration
adjusted for [^{15}O]water decay



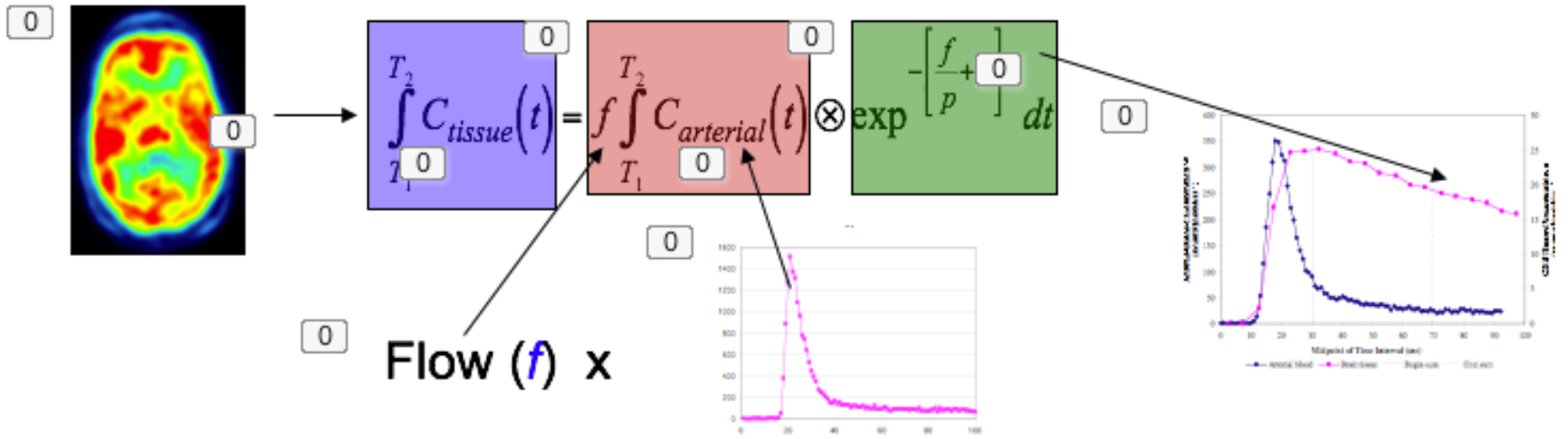
Ponto et al., 2006


r = -0.62
p = 0.003 **
Absolute hippocampal CVR (ml/min/100mL)
25
20
15
10
5
0
5
10
15
cfPWV(m/s)
Covariates: age, sex and MAP

Supplemental

- Assessment of global CBF:
  - [^{15}O]water PET imaging is "gold-standard" for human CBF determinations
  - *Quantitative* measure
  - Water diffuses freely between tissues based on concentration gradient
  - CBF is determined by measuring the [^{15}O]water concentration in tissues by PET imaging
  - Arterial blood by continuous sampling (arterial input function) and combining this information via a mathematical model to create blood flow images
  - 122 second half-life allows for multiple determinations per imaging session

Supplemental



Amount in tissue = blood flow x amount in the arterial blood convolved with the washout (flow and partitioning) and decay.