Significance of White Matter Hyperintensities in MCI

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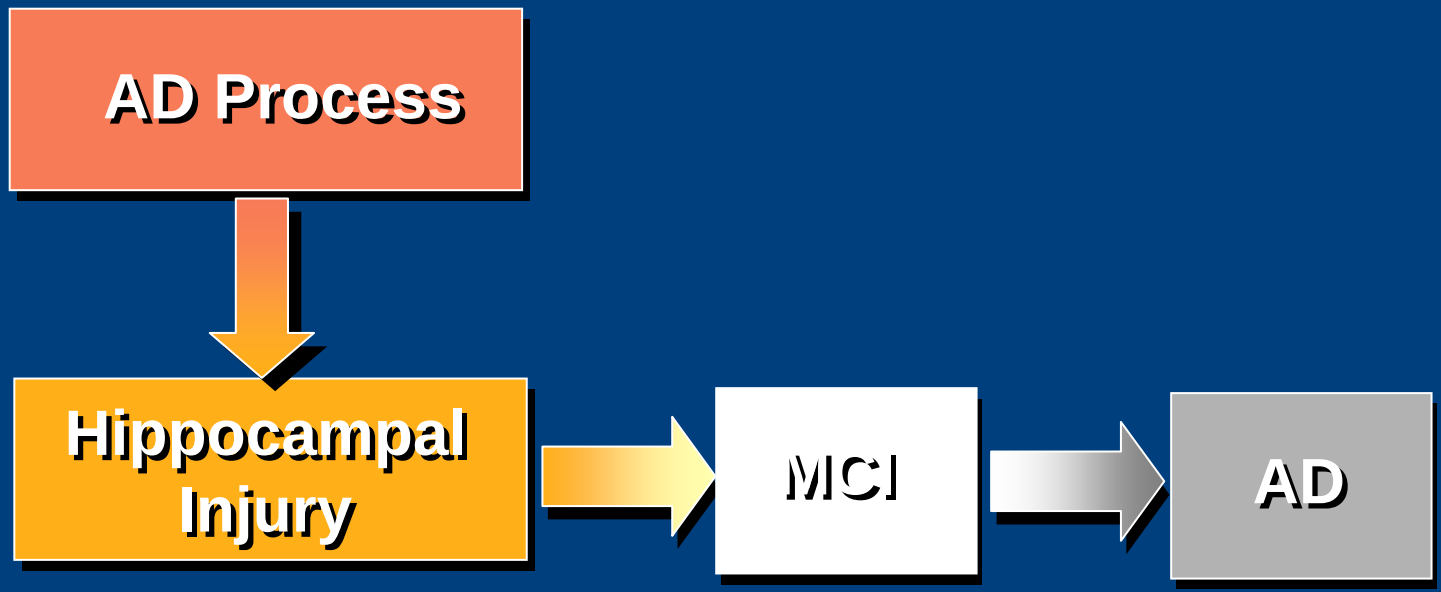
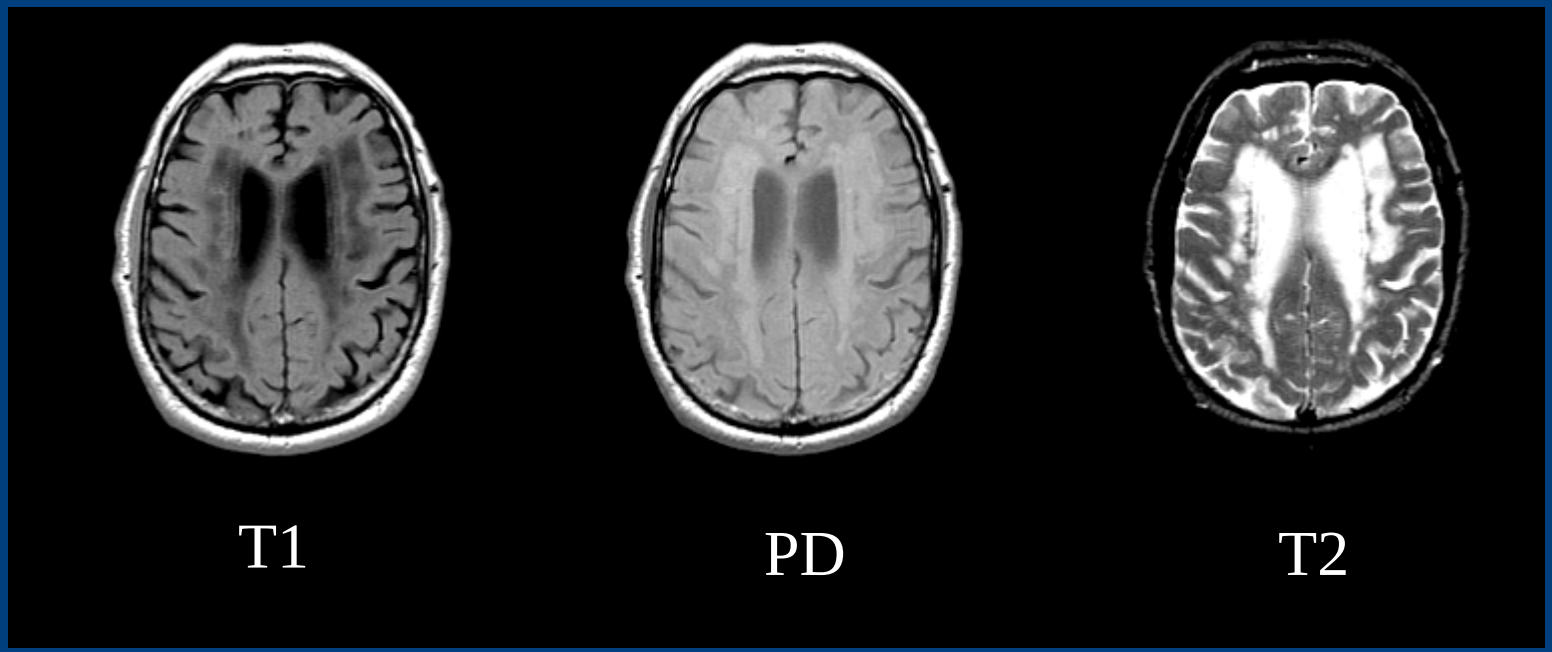
(IDeA) Laboratory

MCI is Early AD



Petersen et al, Arch Neurol, 2001

White Matter Hyperintensities

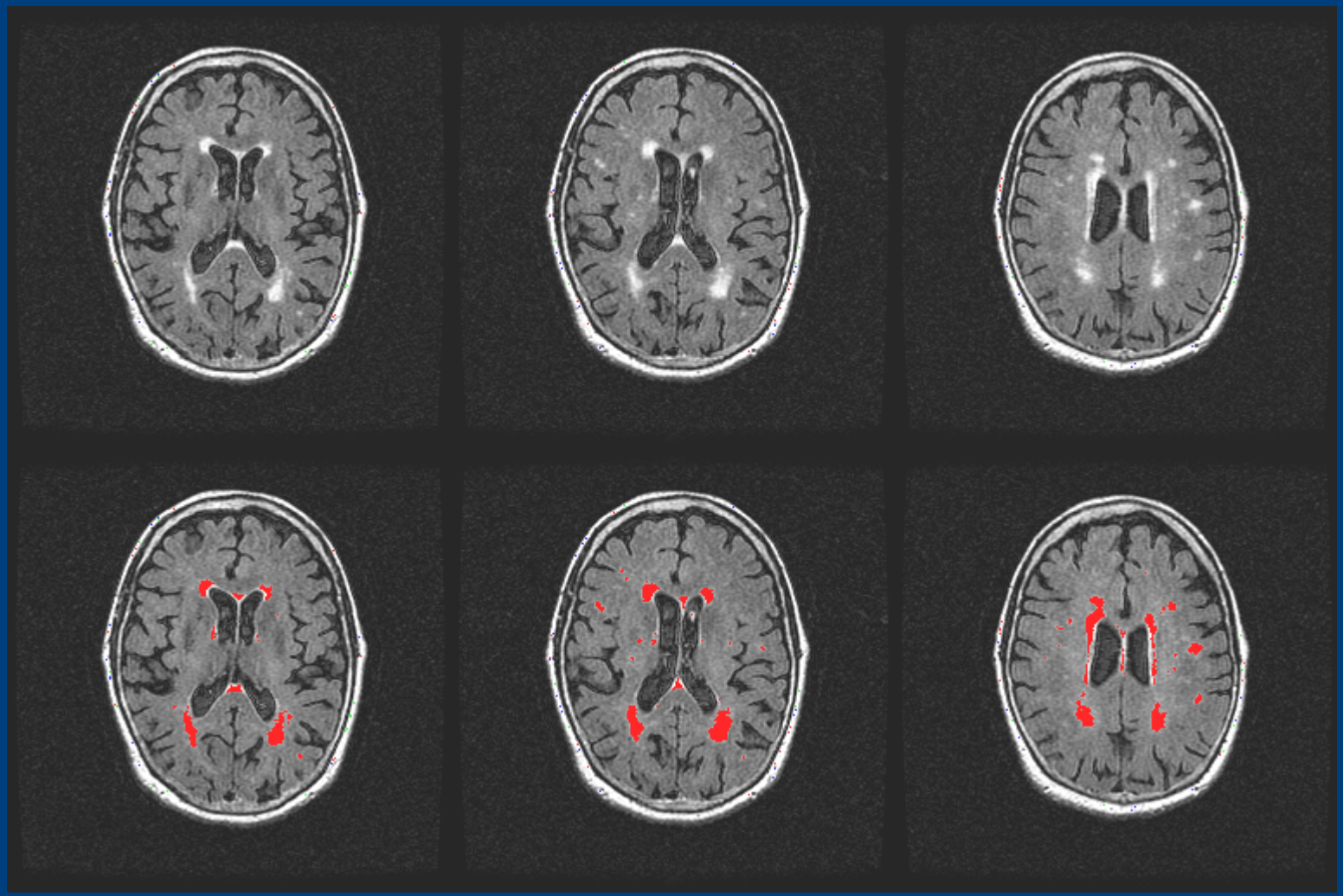


Vascular Risk Factors Predict WMH

Risk Factor	P-value
Age	<0.0001
Diabetes	0.0113
Heart Disease	<0.0001
Systolic Blood Pressure	<0.0001
Left Ventricular Hypertrophy	0.0001
Treated Hypertension	<0.0001

Jeerakathil, et al, Stroke, 2004

WMH Quantification



White Matter Hyperintensities and MCI

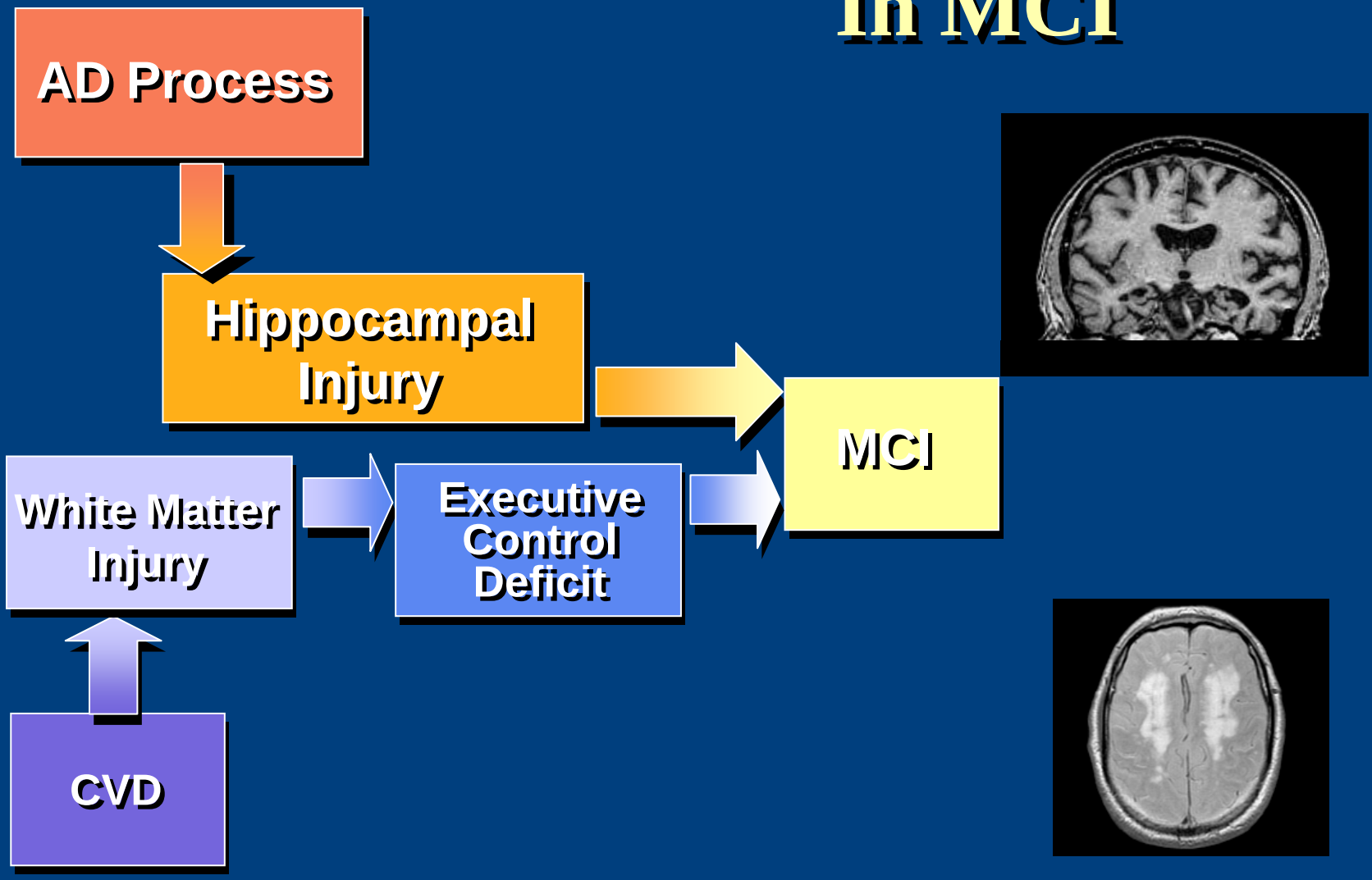
Predictor Variable	Adjusted RR and 95% CL
Age	1.18 [1.03,1.35]
WMH	5.34 [1.80,15.9]
ApoE4	3.54 [1.43,8.78]
Diastolic BP	1.70 [1.07,2.71]

DeCarli et al, Arch Neurol, 2001

WMH are Associated with Episodic Memory Deficits

- DeCarli et al, Arch Neurol, 2001
- Wu et al, Neurology, 2002
- Lopez et al, Arch Neurol, 2003
- Petkov et al, J Int Neuropsychol Soc, 2004

Role of AD and WMH In MCI



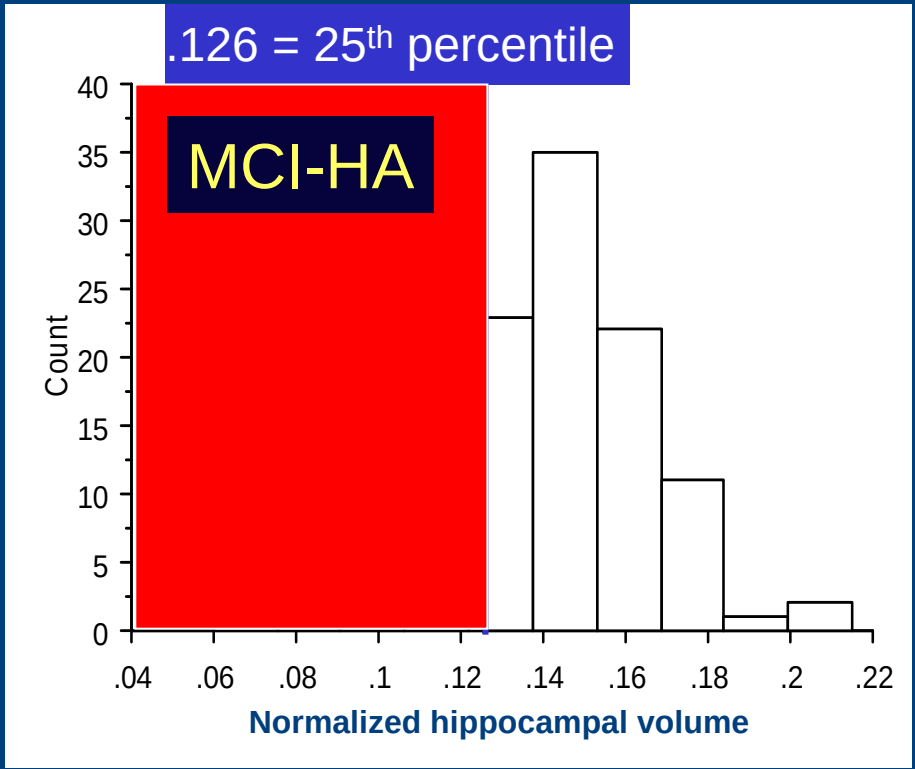
Different Mechanisms of Episodic Memory Failure in MCI

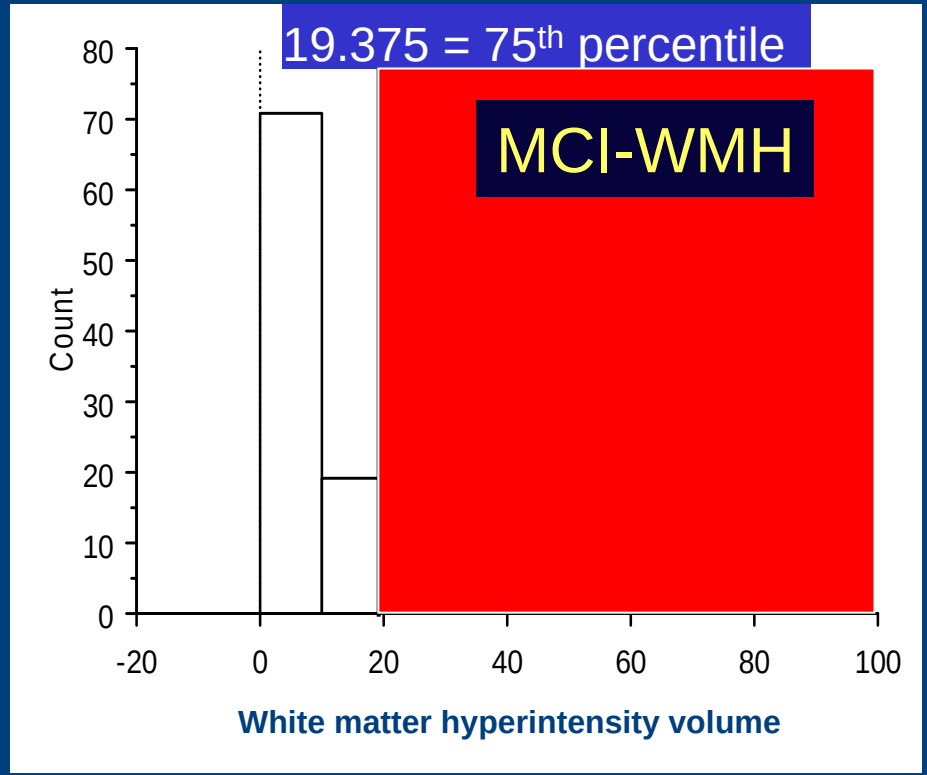
Christine Wu Nordahl, Charan Ranganath, Andrew Yonelinas, Charles DeCarli, Bruce Reed,William J. Jagust

Neuropsychologia 43(11) 1688-1697; 2005

IDeA Lab

aMCI Subtypes





Based on SALSA dataset, n=122

Subject Characteristics

	Controls	MCI-HA	MCI-WMH
n	20	11	11
Age	78.65 (6.34)	74.55 (5.65)	77.64 (3.56)
Education	15.6 (2.79)	15.8 (3.46)	13.5 (1.51)
Gender (M/F)	5/15	4/7	5/6
MMSE	29.63 (0.49)	27.46 (1.81)*	27.27(2.45)*
Left HC	.150 (.03)	.102 (.03)*	.148 (.02)
Right HC	.152 (.02)	.107 (.03)*	.147 (.01)
WMH load	13.15 (15.185)	7.66 (2.93)	34.38 (12.2)*
Hypertension	47%	45%	82%
Type II Diabetes	12%	0%	27%

* differs from other groups, $p < .05$

Behavioral Tasks

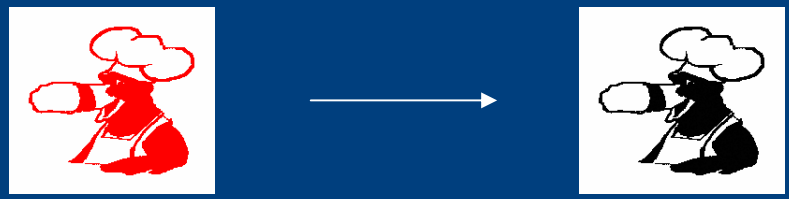
1. Episodic Memory Task: Object-Color Association

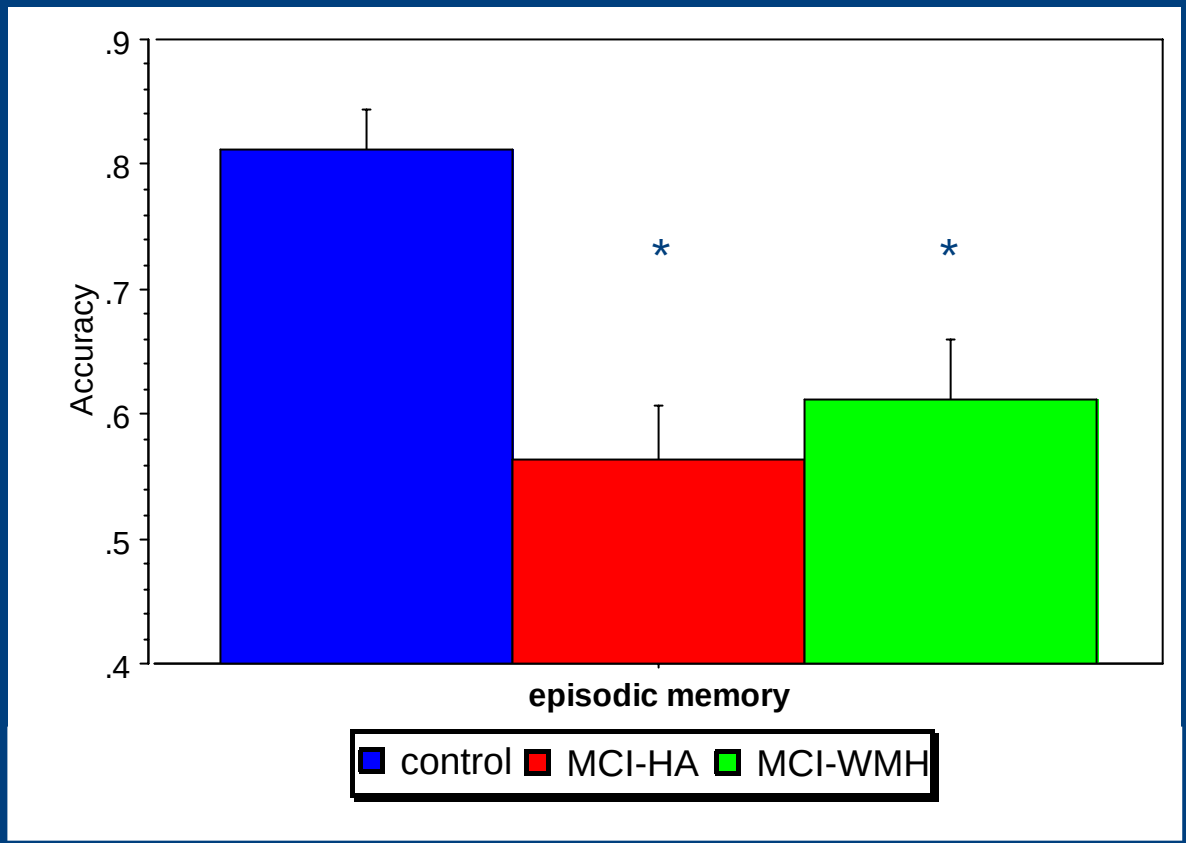
study
18 red/18 green

delay
~60m

test
red or green?

MCI-HA and MCI-WMH are equally impaired on the color association episodic memory task

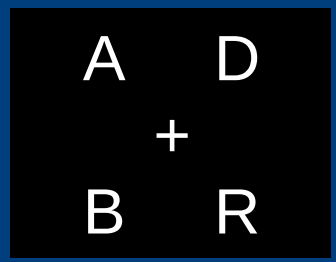




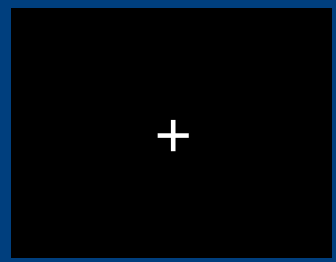
* Differs from controls and MCI-HA p < .01

Behavioral Tasks

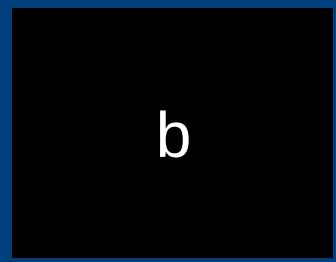
2. Working Memory Task: Item Recognition
   - 2, 4, 6 - item verbal
   - 4 - item spatial



study

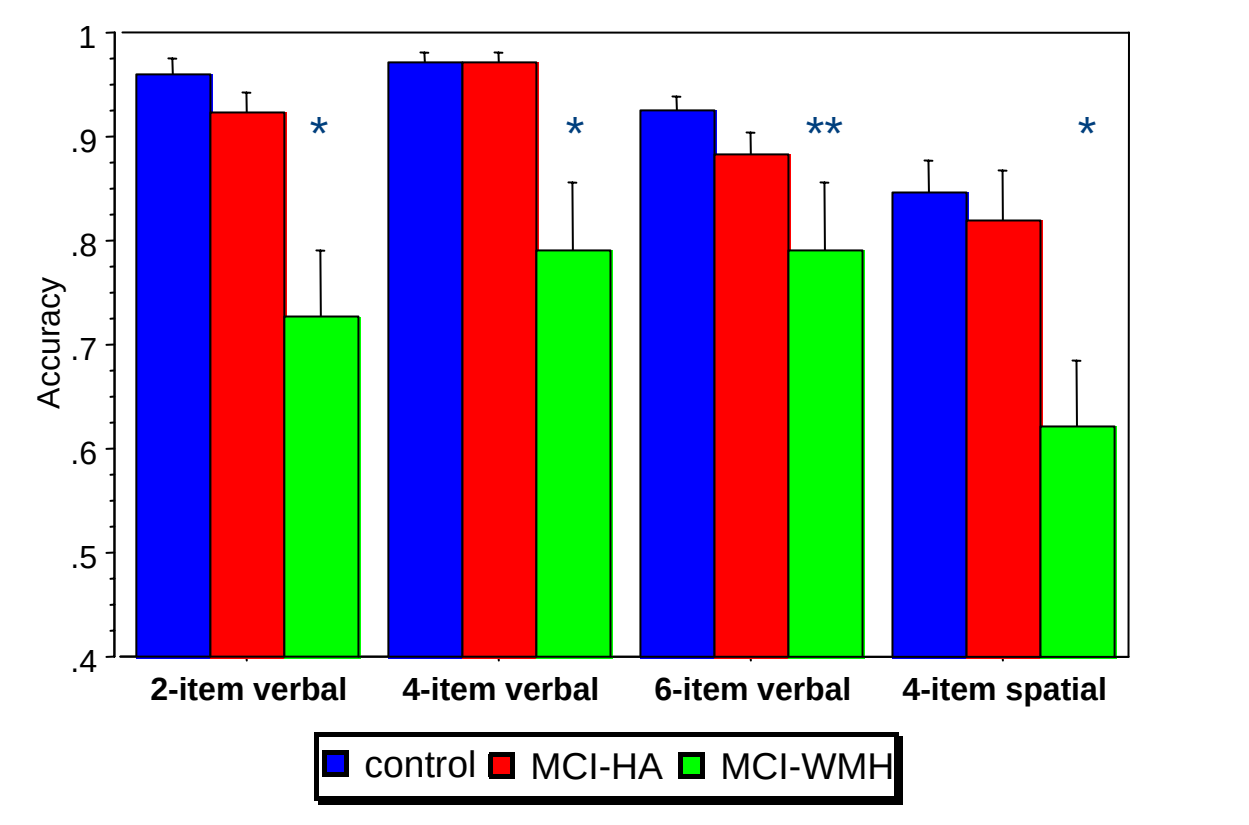


delay
2 sec



probe

MCI-WMH are impaired on the item recognition task

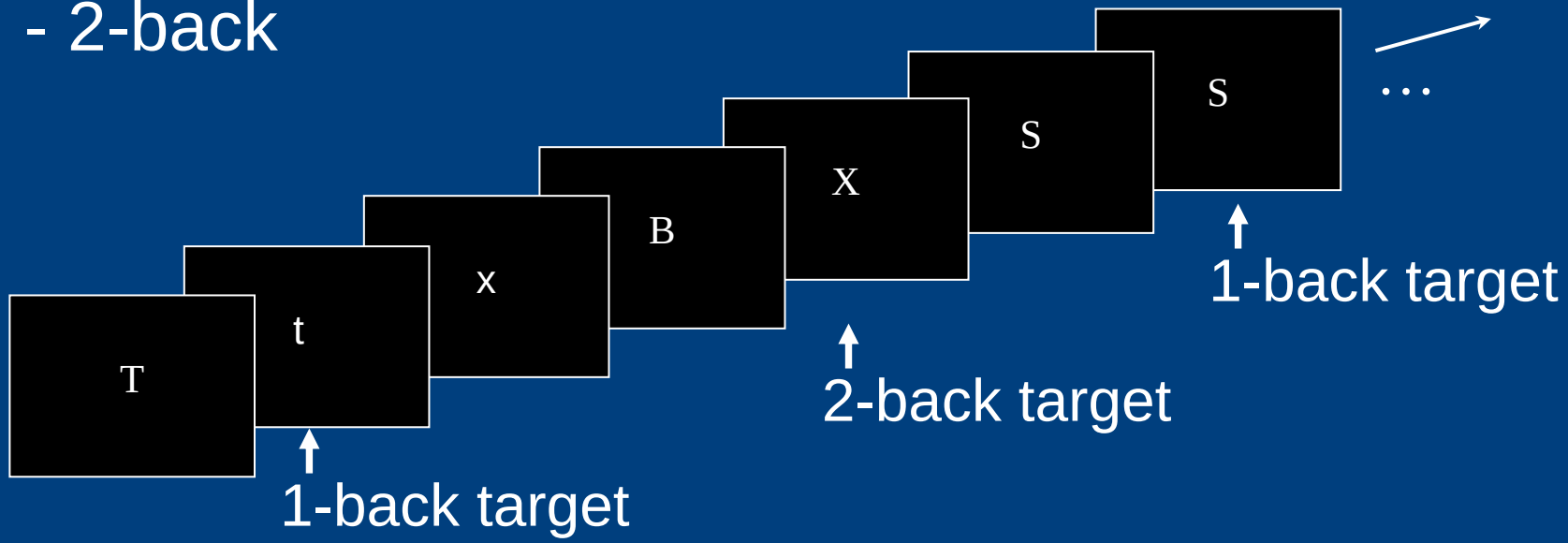


* Differs from controls and MCI-HA p < .01

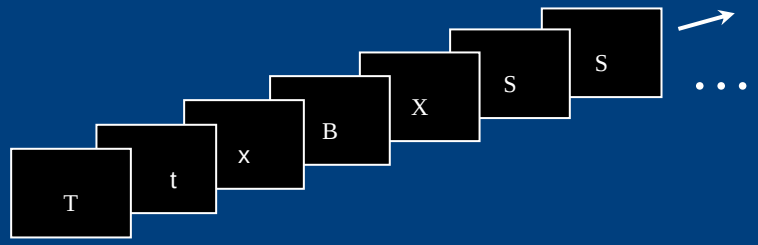
** Differs from controls p < .01, Differs from MCI-HA p = .08

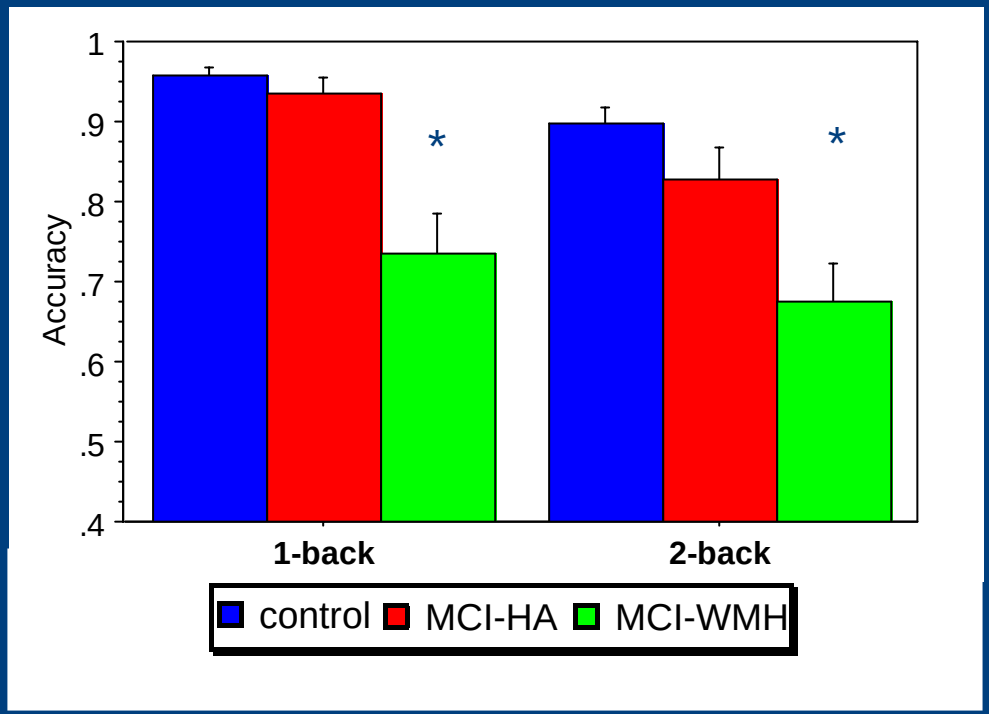
Behavioral Tasks

3. Working Memory Task: N-back
   - 1-back
   - 2-back



MCI-WMH are also impaired on the n-back working memory tasks





* Differs from controls and MCI-HA p < .01

Summary of Behavioral Data

- MCI-HC and MCI-WMH are equally impaired on the episodic memory task

- MCI-WMH are impaired on working memory, both in simple maintenance as well as a more complicated task involving manipulation and maintenance

White Matter Changes Compromise Prefrontal Cortex Function in Healthy Elderly

Christine Wu Nordahl, Charan Ranganath, Andrew Yonelinas, Charles DeCarli, Evan Fletcher,William J. Jagust

In Press: Journal Cognitive Neuroscience

IDeA Lab

Behavioral Tasks

Episodic Retrieval

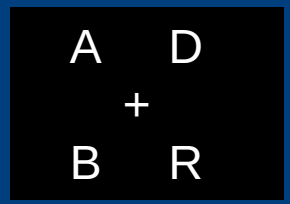
Study (prior to scanning)
18 red/18 green

delay
~60m

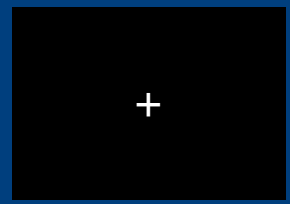
Test (during scanning)
red or green?

Working memory:

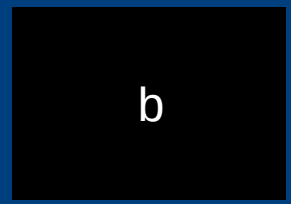
Low and high loads



study

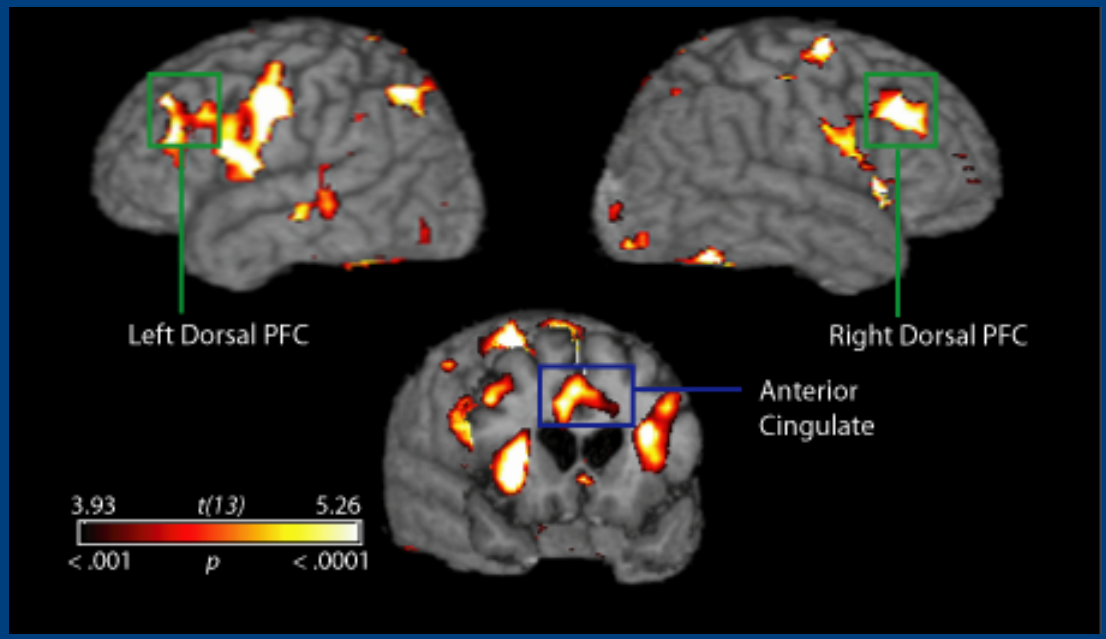


delay
2 sec



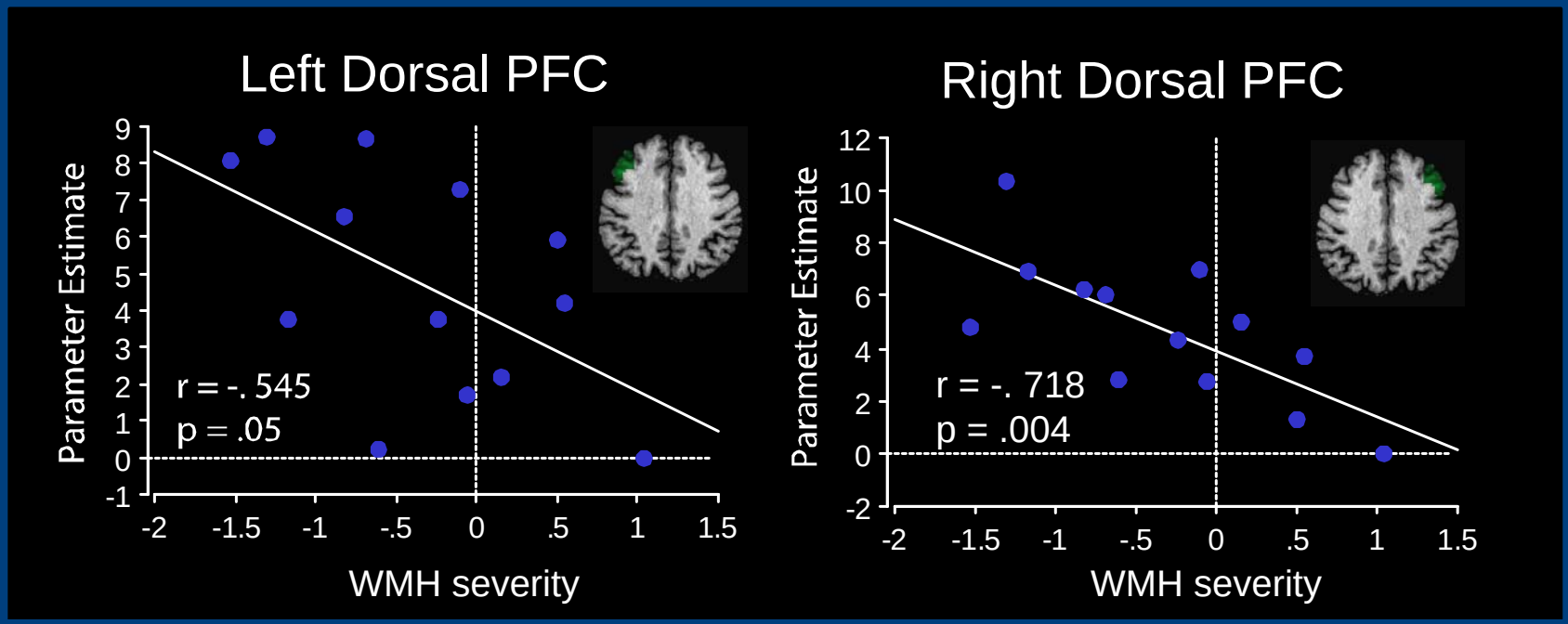
probe

Working memory activations



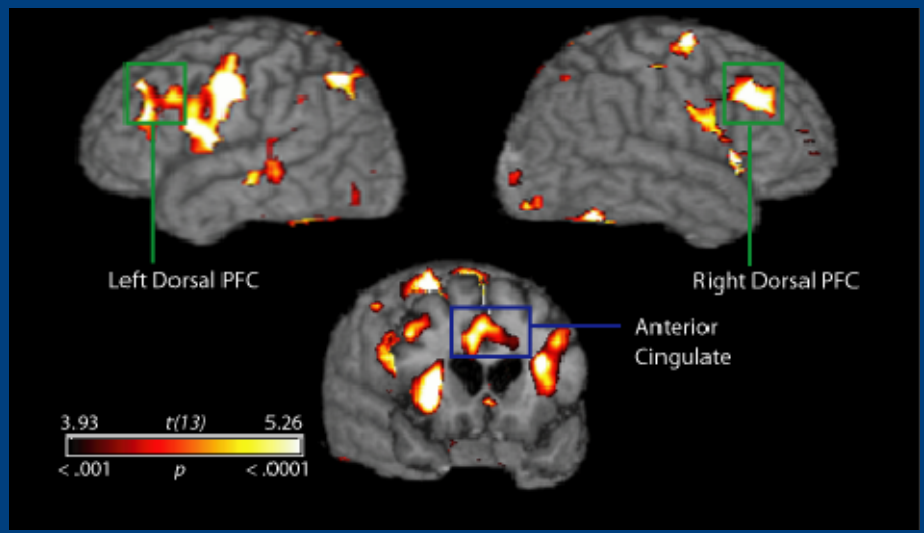
- Bilateral dorsal prefrontal cortex activations
- Bilateral ventral prefrontal cortex activations

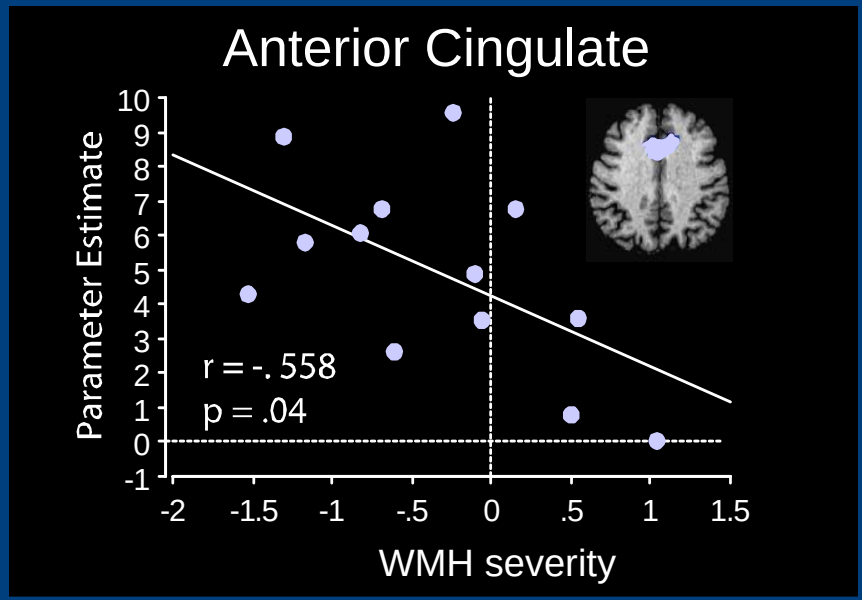
Working memory task:
Dorsal prefrontal cortex function is negatively correlated with WMH severity



Consistent with evidence suggesting that dorsal PFC is more affected in aging

Working memory task:
Anterior cingulate cortex function is negatively correlated with WMH severity





Anterior cingulate activity is associated with cognitive control (ie. ability to guide thought and action in accordance with internal intentions)

Functional connectivity between anterior cingulate and PFC mediates successful task performance (Kondo et al 2004)

Summary of fMRI Data

- WMH a presumed indicator of cerebrovascular brain injury is associated with working memory impairment
- Executive control processes are likely involved and related to amount of WMH

Disconnection of Working Memory Processes by White Matter Hyperintensities

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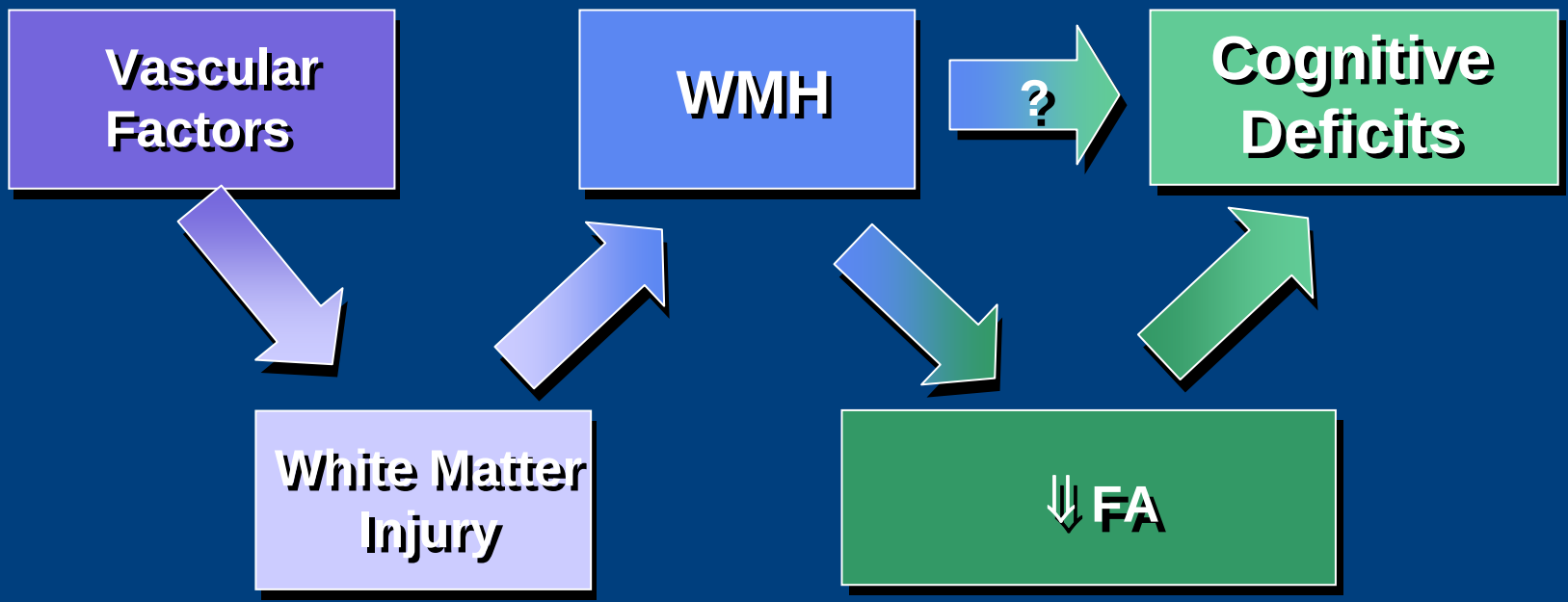
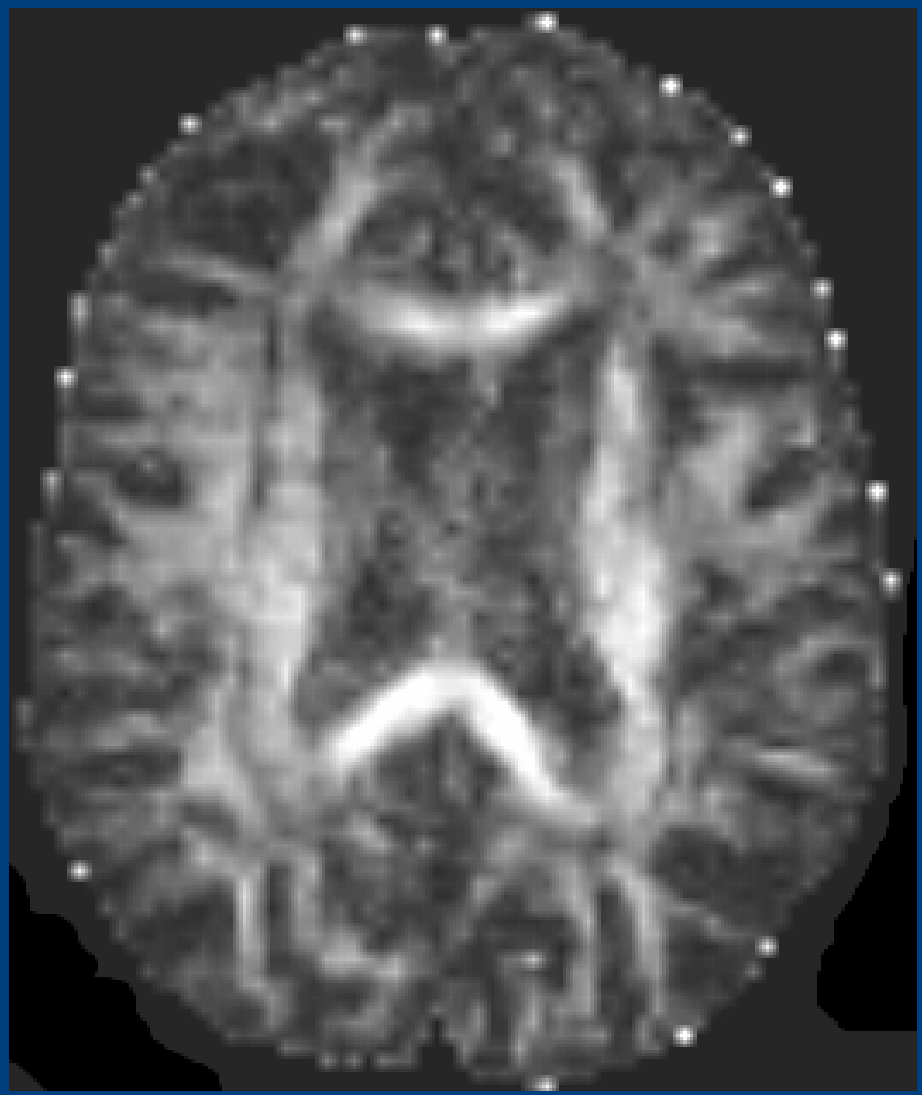
University of California at Davis

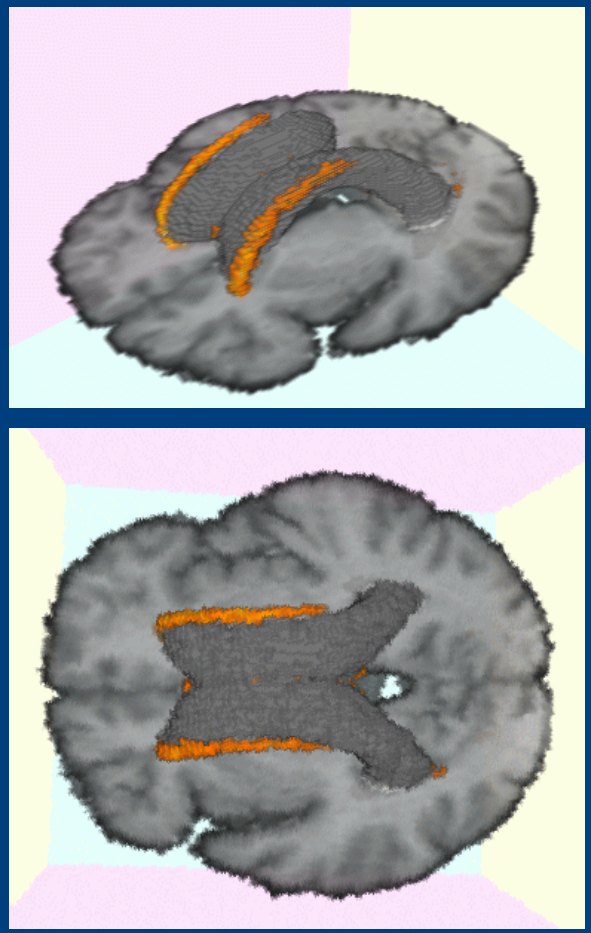
Disconnection Hypothesis



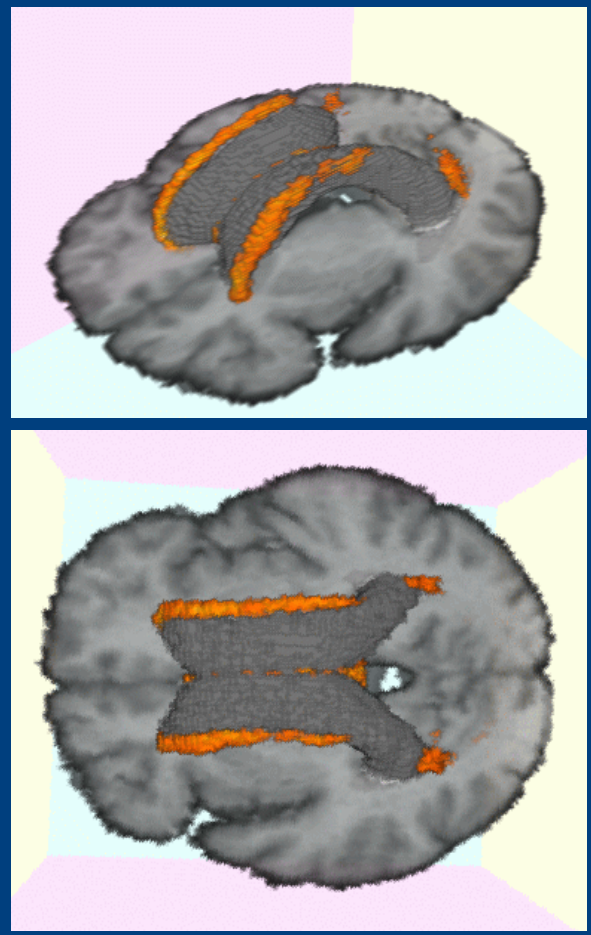
Anisotropy Mapping



Location of WMH in MCI

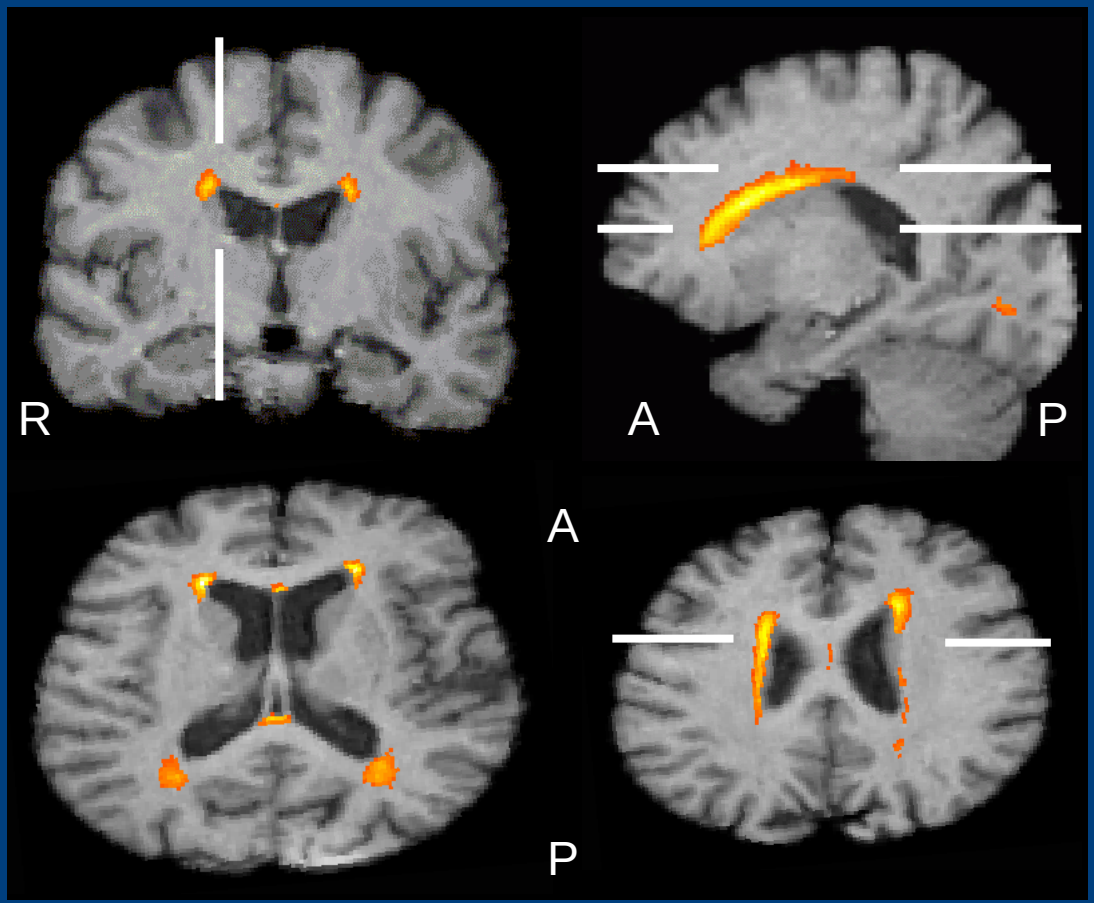


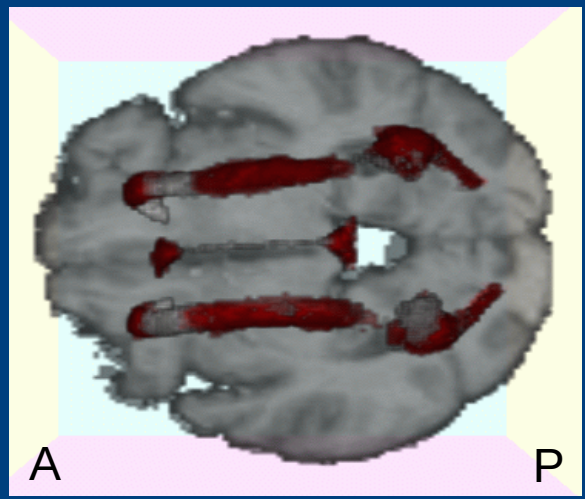
Normal Controls (n=30)



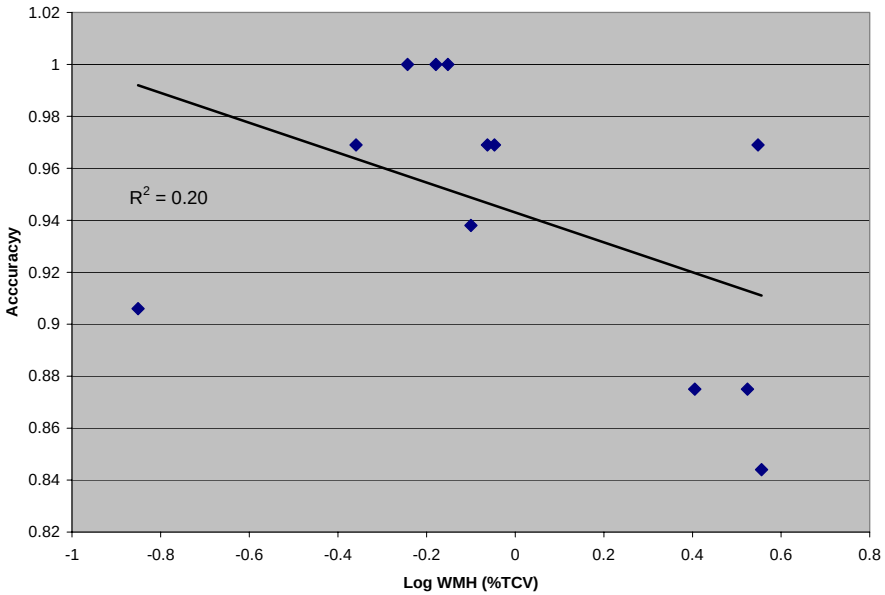
MCI (n=29)

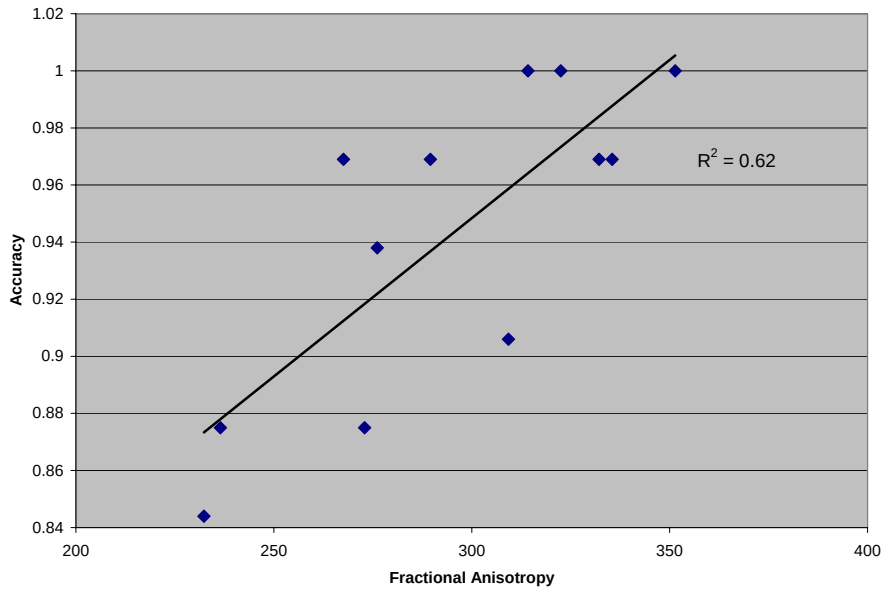
Location of WMH and ROI





Correlations





Total WMH

FA within WMH

Summary

- aMCI has at least 2 subtypes
  - Hi WMH
  - Small Hippocampi
- Amnesia in MCI-WMH results from
  - Impairments in executive control
  - Reduced prefrontal activation
  - Disconnection from posterior targets

Conclusions

- WMH are common to the elderly
- WMH alone can be associated with episodic memory impairments
- WMH likely contribute to susceptibility to late life cognitive impairment and dementia
- WMH are potentially modifiable

IDeA Lab

Imaging of Dementia and Aging

- Adriane Mayda
- Christine Nordahl
- Evan Fletcher
- Owen Carmichael
- IDeA Lab

Supported by NIH:
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http://neuroscience.ucdavis.edu/idealab/