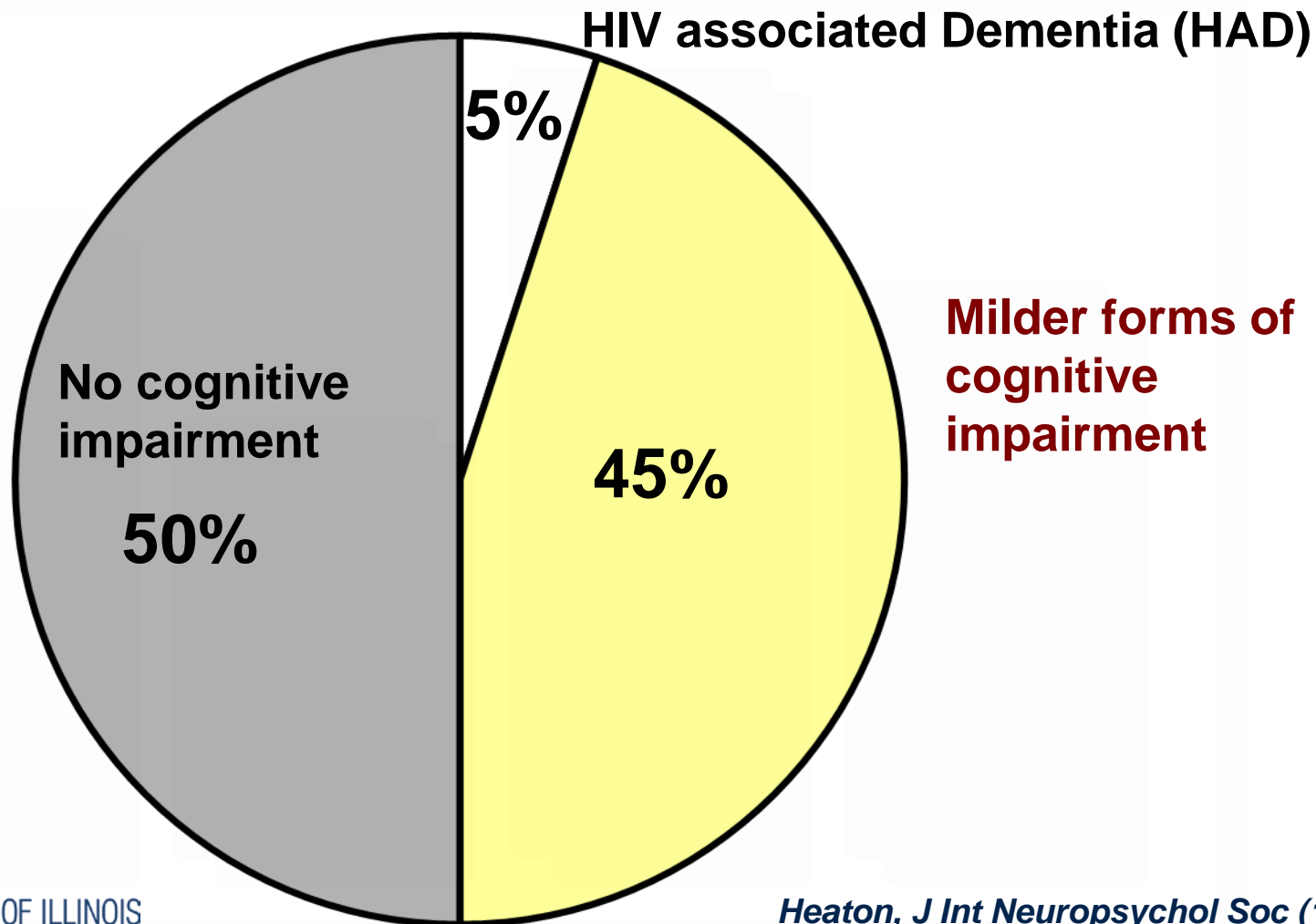


# Perceived stress influences prefrontal cortex function in midlife women with HIV infection

**Leah H. Rubin**, Minjie Wu, Vanessa J. Meyer, Erin E. Sundermann, Rhoda Conant, Rachael Smith, Sheila D'Sa, Kathleen M. Weber, Mardge H. Cohen, Deborah M. Little, & Pauline M. Maki

# Importance of identifying risk factors of cognition dysfunction in HIV

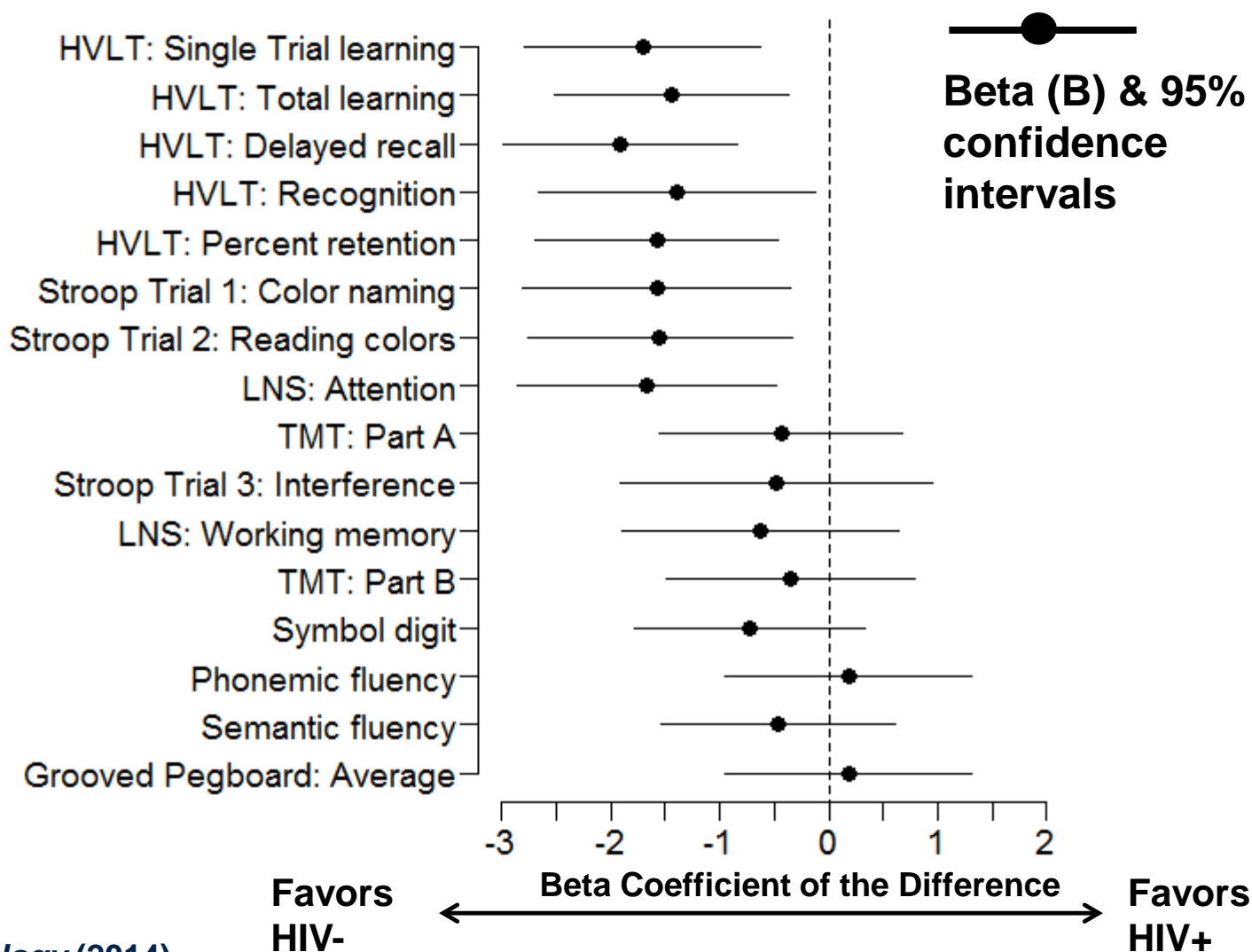


*Heaton, J Int Neuropsychol Soc (1995);  
Heaton, Neurology (2010)*

# HIV+ women show deficits in verbal learning and memory compared to at-risk HIV- women

**Verbal Learning & Memory**

**Attention & Concentration**



N=1521

# Verbal Learning and Memory

Broom

Ham

Pencil

Chicken

Notebook

Sponge

Turkey

Detergent

Scissors

Hamburger

Bleach

Eraser

# Verbal Learning and Memory

**Broom**

**Ham**

**Pencil**

**Chicken**

**Notebook**

**Sponge**

**Turkey**

**Detergent**

**Scissors**

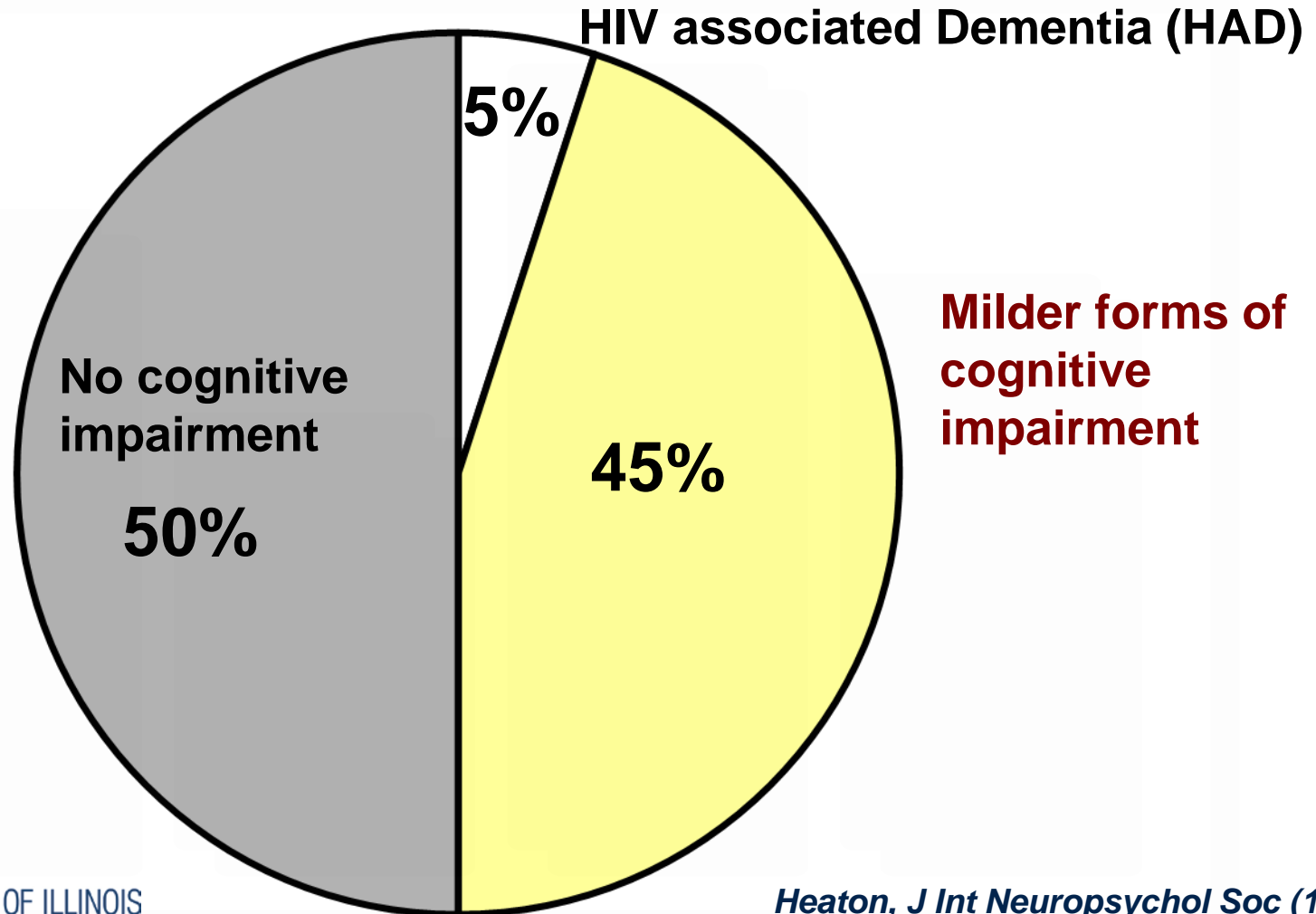
**Hamburger**

**Bleach**

**Eraser**

Categories
Household items
Food
School supplies

# Importance of identifying risk factors of cognition dysfunction in HIV



*Heaton, J Int Neuropsychol Soc (1995);  
Heaton, Neurology (2010)*

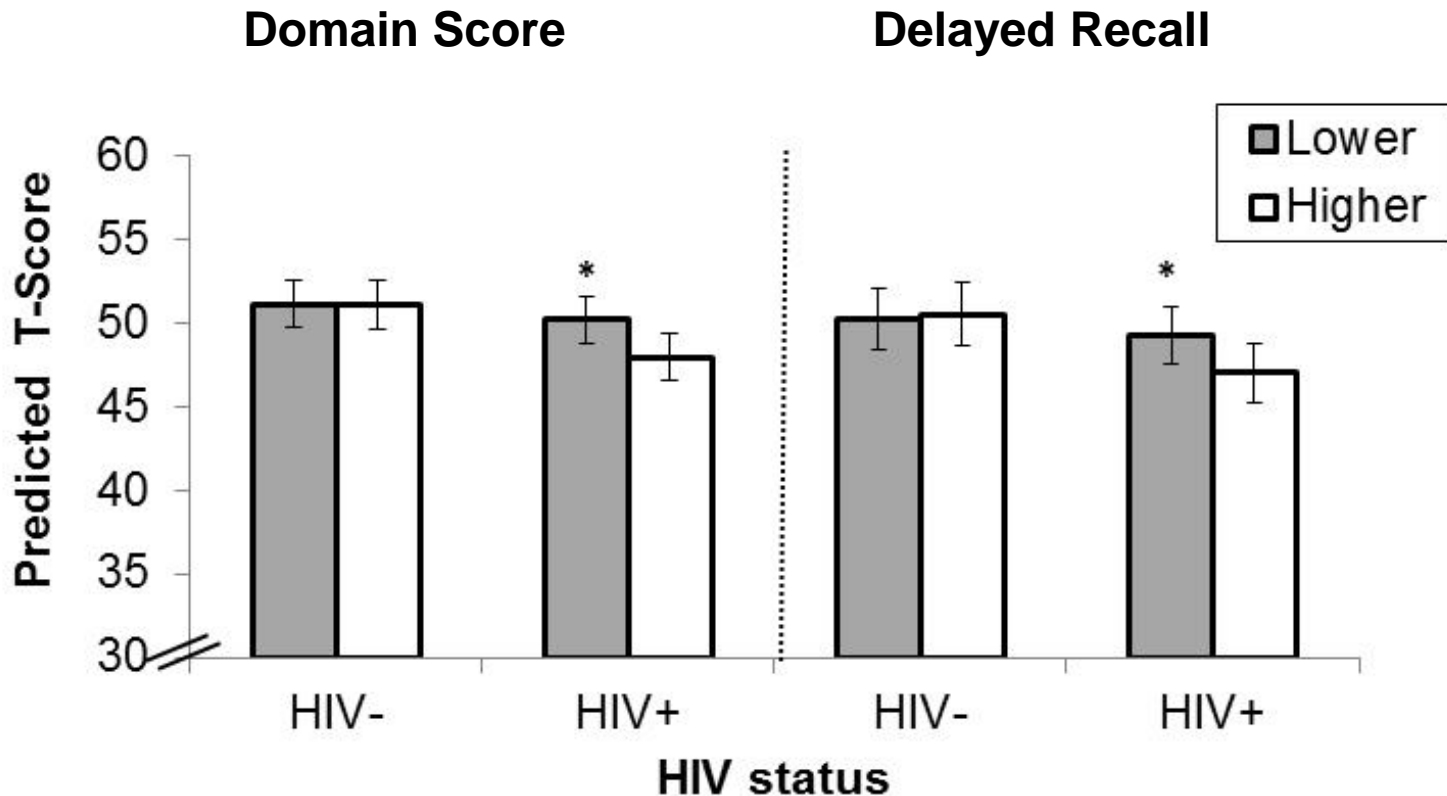
# Why study stress as a contributor to verbal memory deficits in HIV+ women?

## Negative life stressors:

- Prevalent in HIV+ individuals particularly women
- Risk factors for mood/anxiety disorders
- Impact physiologic systems (e.g., stress response system)
- Influence cognition and brain function
- Women are differentially vulnerable to cognitive effects of stress hormones compared to men

*Cohen, Am J Public Health (2000); Machtiger, AIDS Behav (2012); Kendler, Archives of Gen Psych (2000); Kessler, Arch Gen Psychiatry (1995); Ciesla, Am J of Psychiatry, (2001); McEwan, Eur J Pharmacol (2008)*

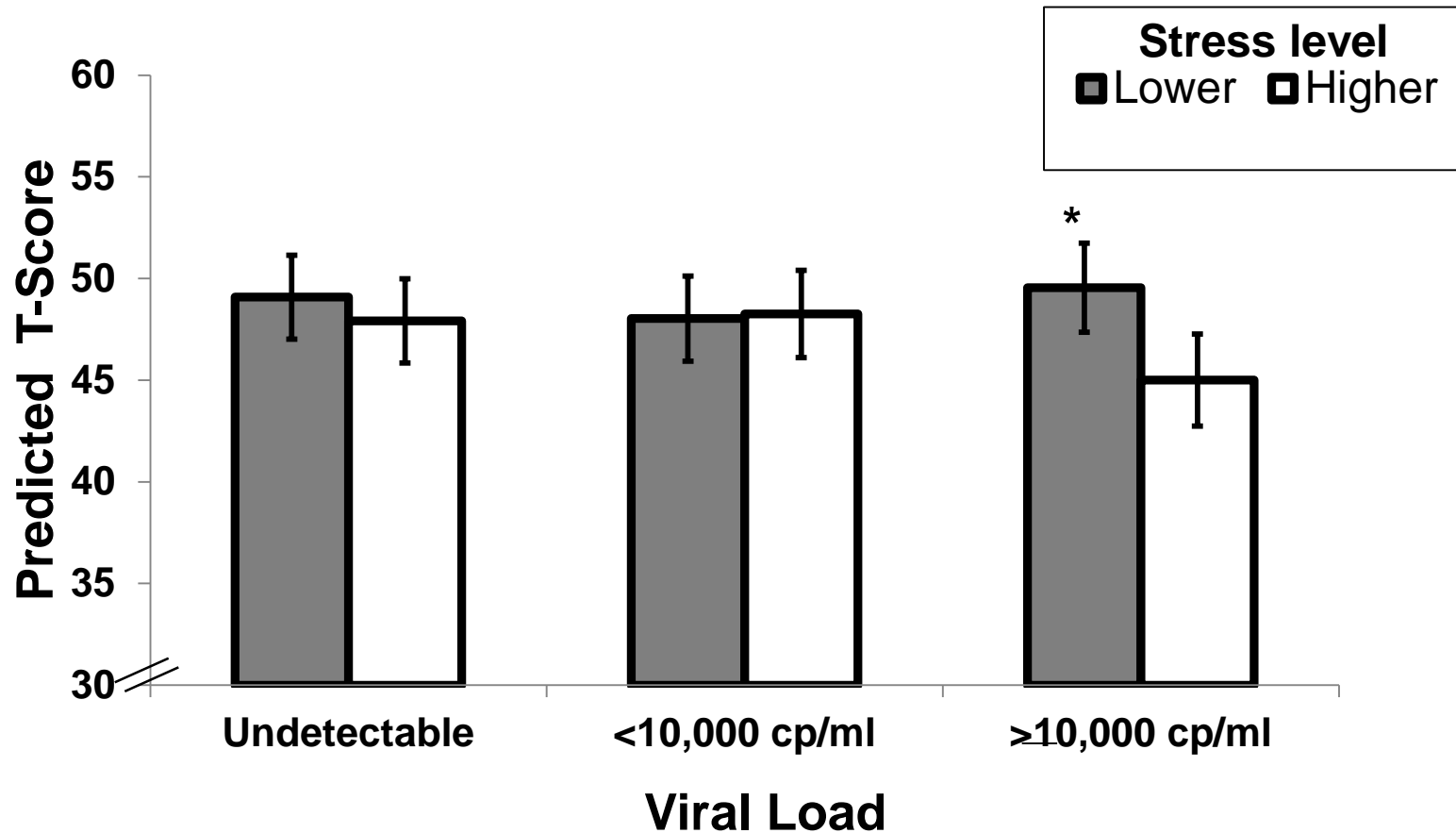
# Perceived stress (higher vs. lower) is associated with the verbal memory domain and delayed recall only in the context of HIV



Note. \* $p < 0.001$ .  $N = 1499$ . Perceived Stress measured with Perceived Stress Scale-10—how unpredictable, uncontrollable, and overloaded respondents find their lives in *past month*. Higher stress  $\geq 18$  (top tertile).



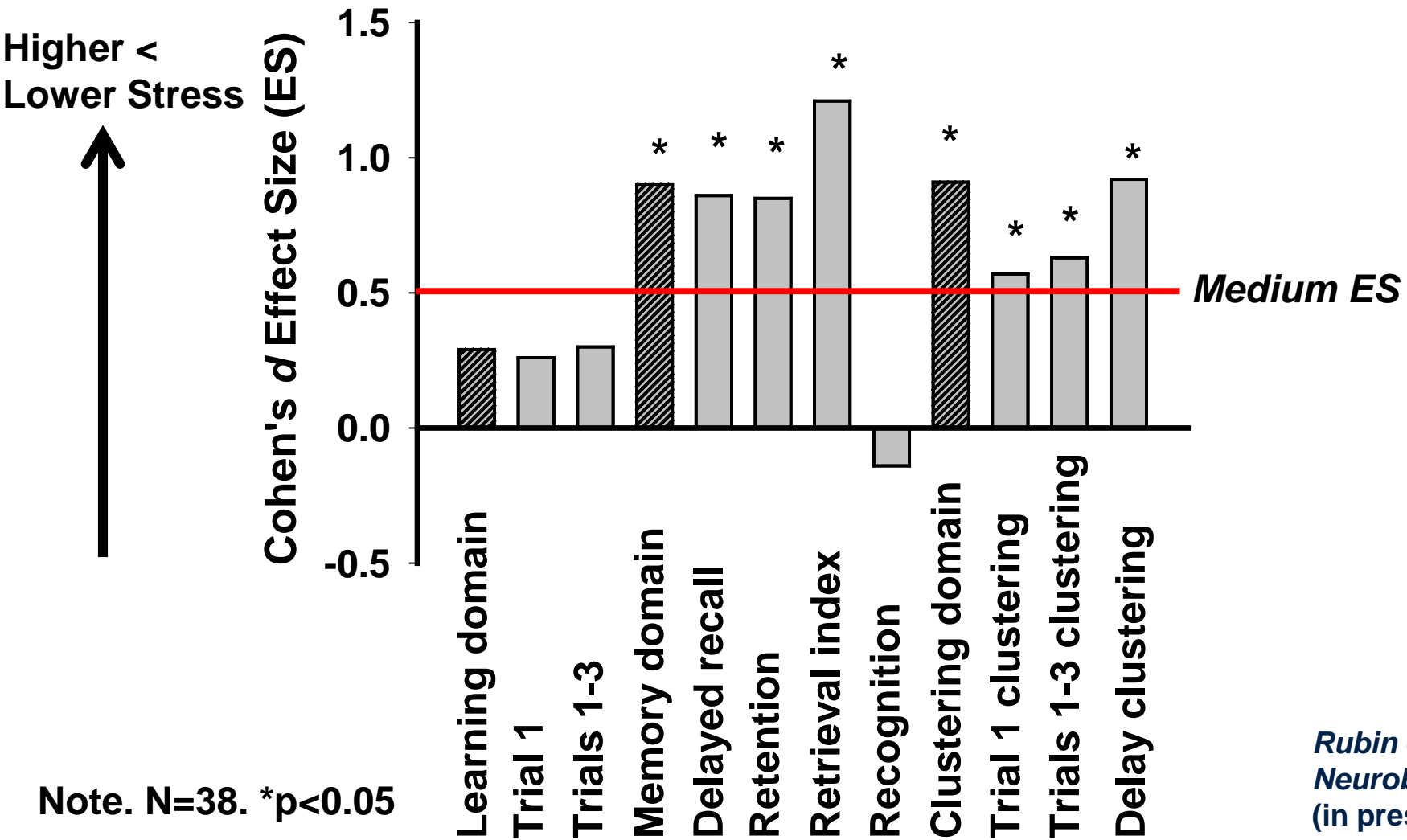
# Association between perceived stress and worse verbal memory in HIV+ women with high viral load



Note. \* $p < 0.001$ . N=1003.

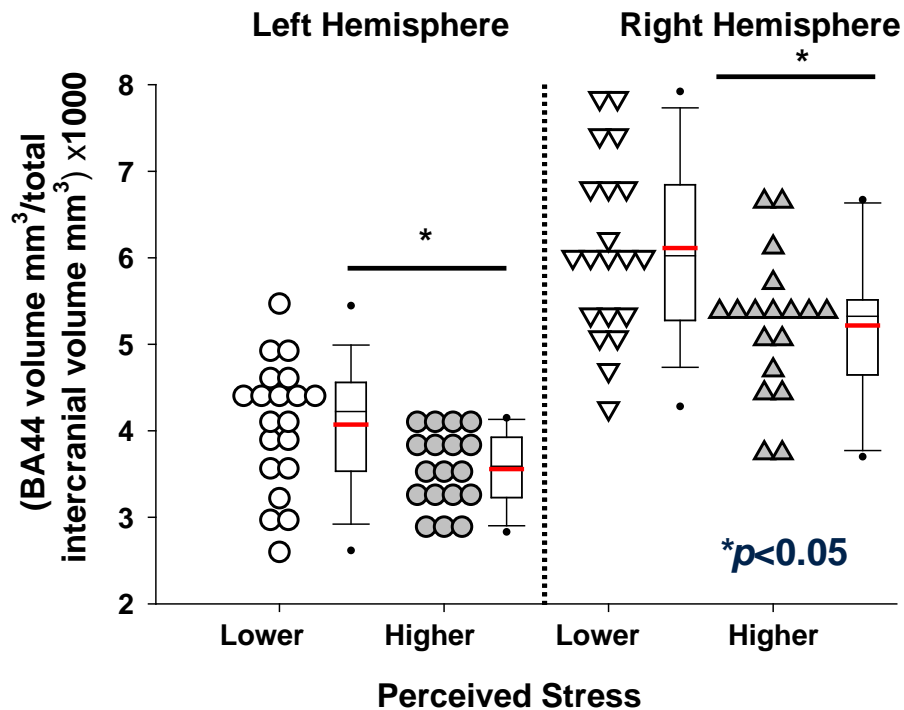
Rubin et al., *J. Neurovirology* (2015)

# In HIV+ women, perceived stress is negatively associated with verbal memory and strategic encoding on the HVLT

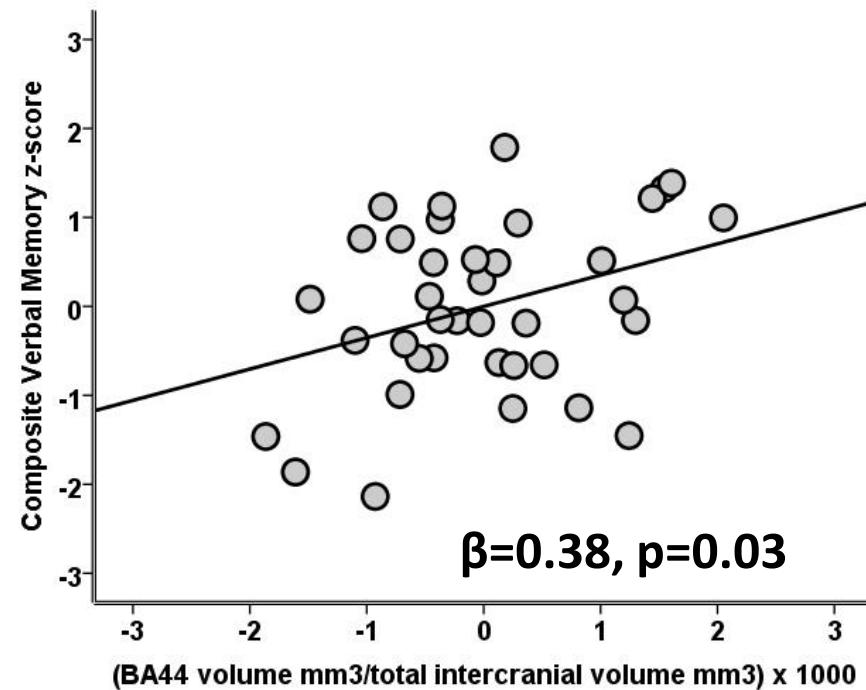


# Prefrontal volumes in the right hemisphere are associated with verbal memory

(A) decreased brain volume



(B) volume-memory association



Note. \* $p<0.05$ . (A) Same pattern seen for middle and superior frontal gyri; (B) Partial plot from regression analysis controlling for age. Same pattern seen on percent retention, delayed free recall, and retrieval index ( $p$ 's $<0.05$ ). Right middle frontal gyrus associated with strategic encoding ( $p$ 's $<0.05$ ).

# Aim

To further understand the neural basis of this stress-related memory impairment, we examined the effects of stress on activation of the prefrontal cortex and strategic encoding during a verbal memory task in a sample of HIV+ midlife women

# Chicago WIHS Participants

	Perceived Stress	
	Lower (n=18), n (%)	Higher (n=18), n (%)
Age, <i>M (SD)</i>	42.56 (6.32)	44.89 (7.67)
Years of Education, <i>M (SD)</i>	12.94 (2.15)	12.14 (2.26)
Black, non-Hispanic	18 (100)	17 (94)
Currently smoking	8 (44)	7 (39)
Recent heavy alcohol use	3 (17)	2 (11)
Recent marijuana use	3 (17)	3 (17)
Ever use cocaine	13 (72)	12 (60)
CD4 <200	2 (12)	3 (17)
Viral load $\geq 10,000$	2 (11)	5 (28)
HAART $\geq 95\%$ compliance	12 (67)	12 (67)

Note. “Recent” refers to within 6 months of the most recent WIHS visit; Heavy alcohol use reflects >7 drinks/wk or >4 drinks in one sitting; HAART, highly active antiretroviral therapy.

# In-scanner verbal memory task

## Encoding

- 30 items
- 5 semantic categories

## Free recall

- After 12-minute delay

## Recognition

- 60 items
- Related and unrelated distractors

Categories
Fruits
Body parts
Furniture
Insects
Natural formations

# In-scanner verbal memory task

## Block design

- 3 second presentation

## Experimental block

- Single presentation →

Pear  
Lake  
Banana  
Head  
Mountain  
Toe

## Control block

- Repeated presentation →

Sailboat  
Sailboat  
Ballet  
Sailboat  
Ballet  
Ballet

Note. Each experimental block contained 1 or 2 words from each semantic category so that clustering occurs within and across blocks.

# Behavioral outcome measures

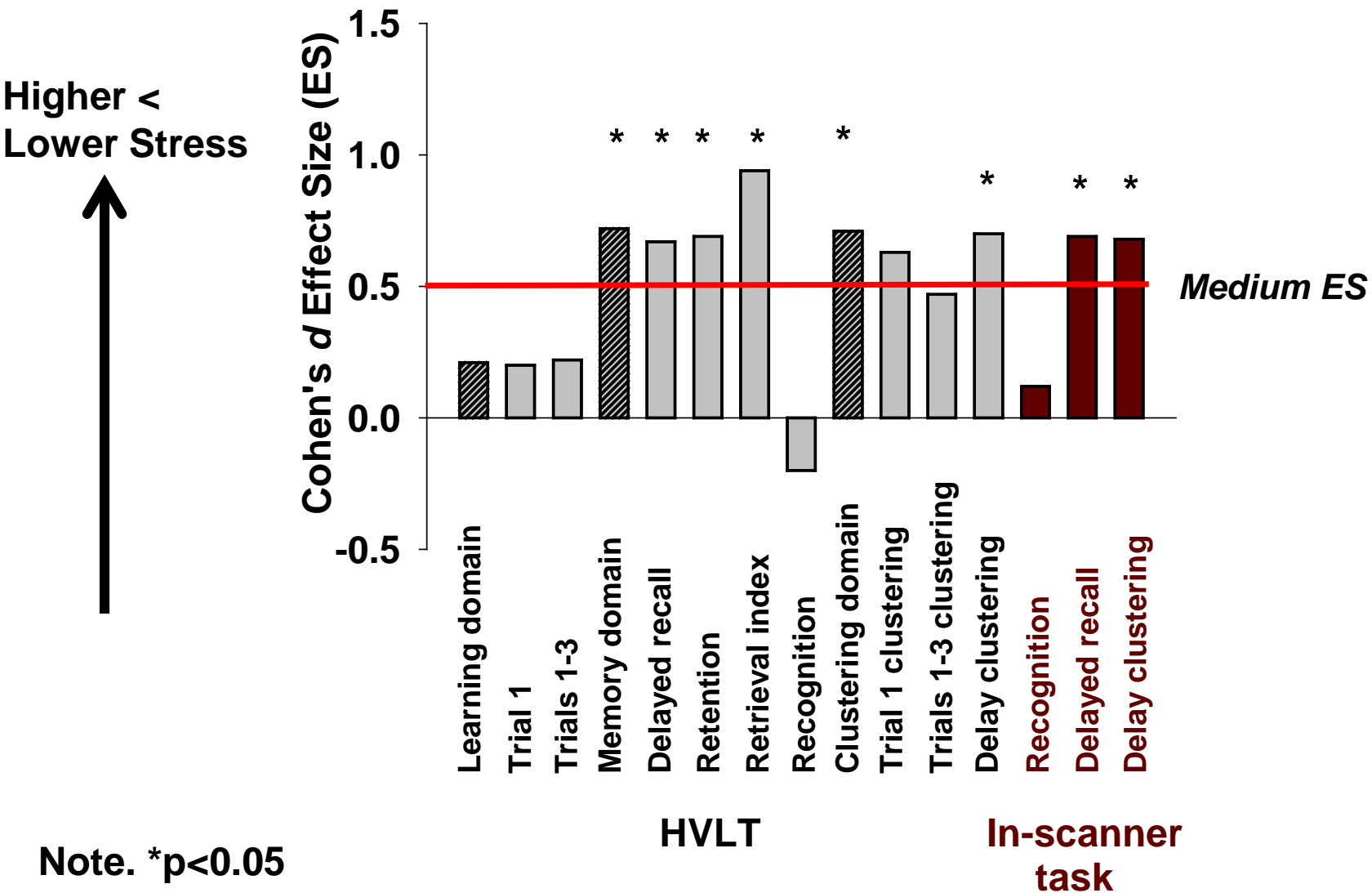
## In-scanner verbal memory task

- Free recall total
- Semantic clustering
- Recognition (% correct)

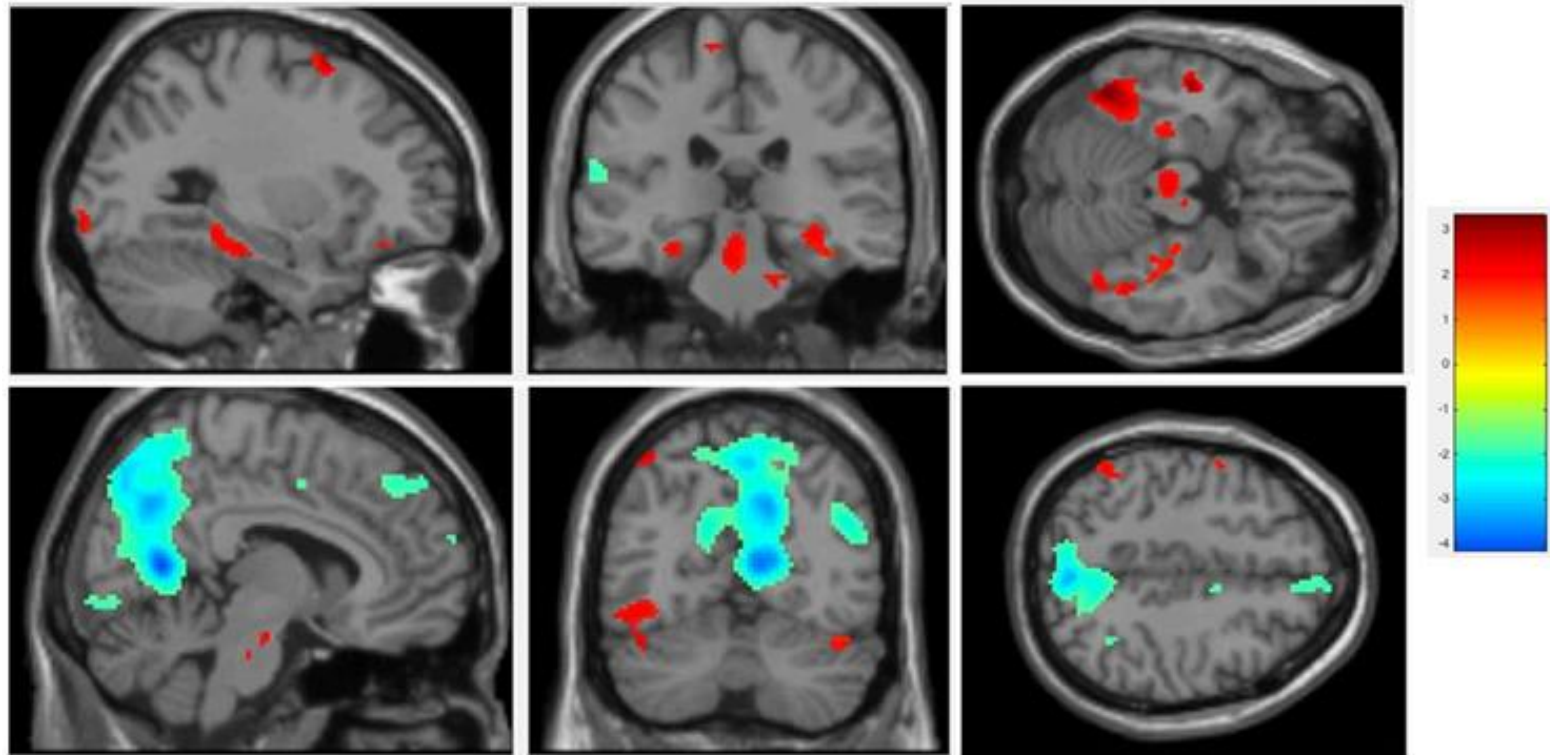
## Hopkins Verbal Learning Test (HVLT)



# In HIV+ women, perceived stress is negatively associated with verbal memory and strategic encoding



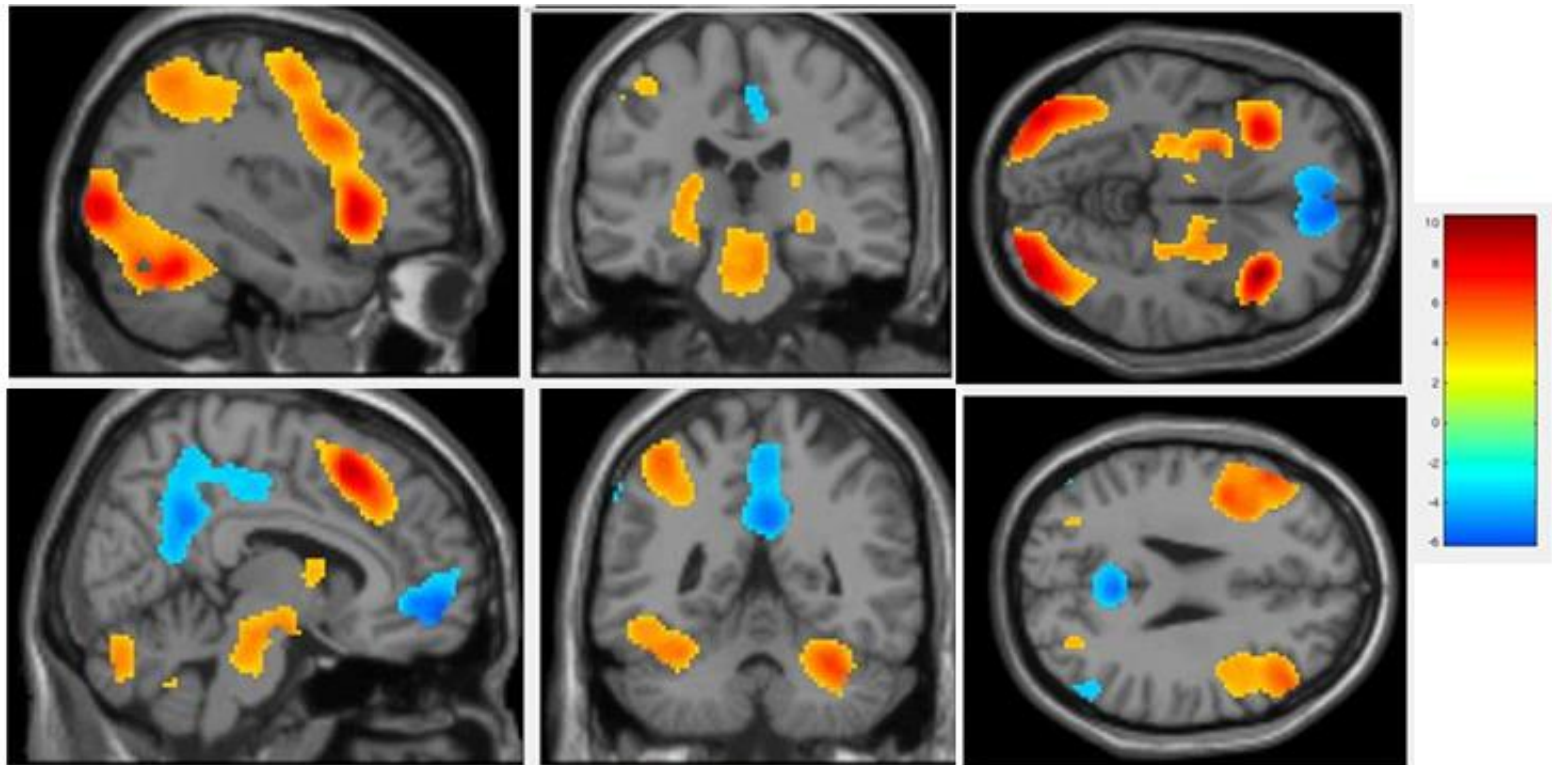
# Encoding Typical Pattern: lower stress + higher stress (n=36)



- Activation of bilateral parahippocampi
- Deactivation of the default mode network

Note. Encoding of novel words (experimental condition) minus repeated encoding of the same two words (control condition),  $p < 0.05$ ,  $k \geq 10$ .

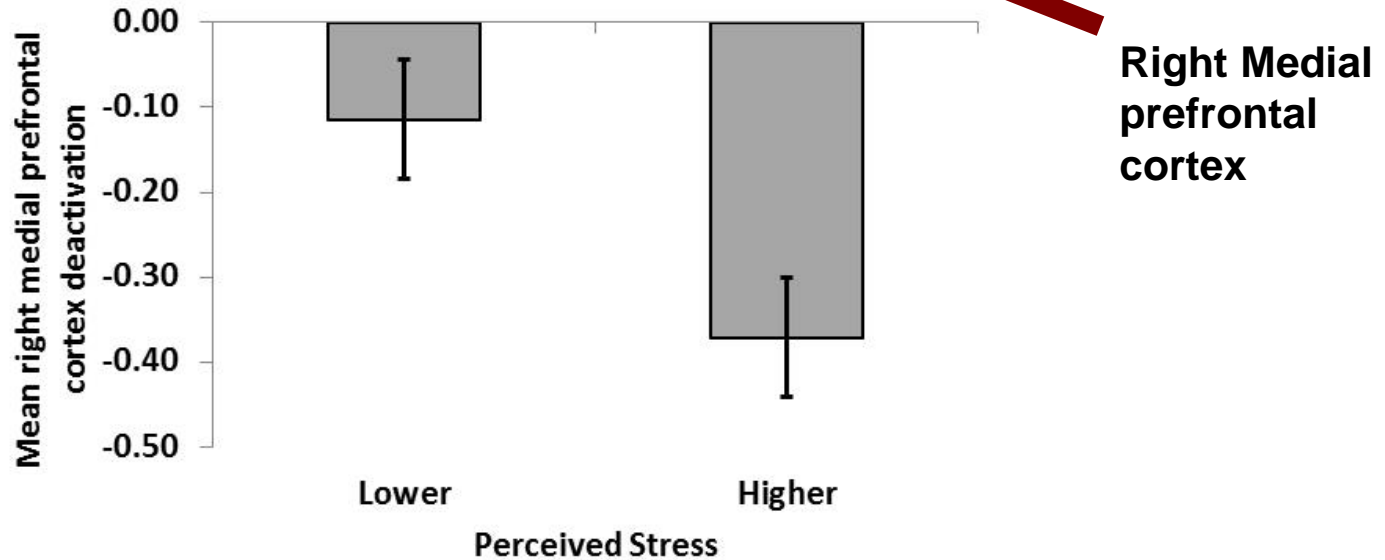
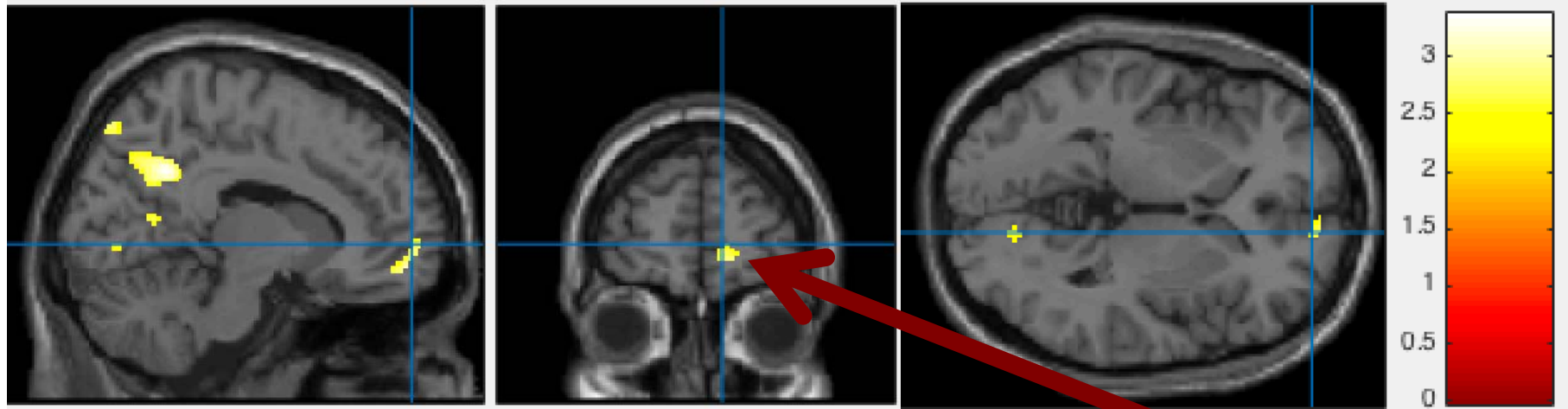
# Recognition Typical Pattern: lower stress + higher stress (n=36)



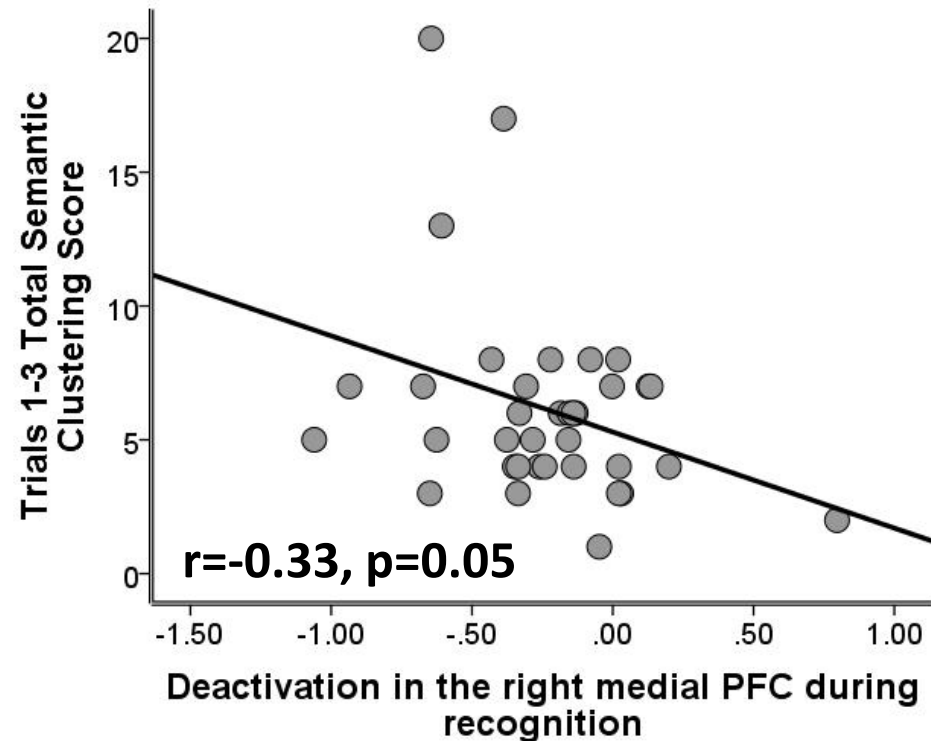
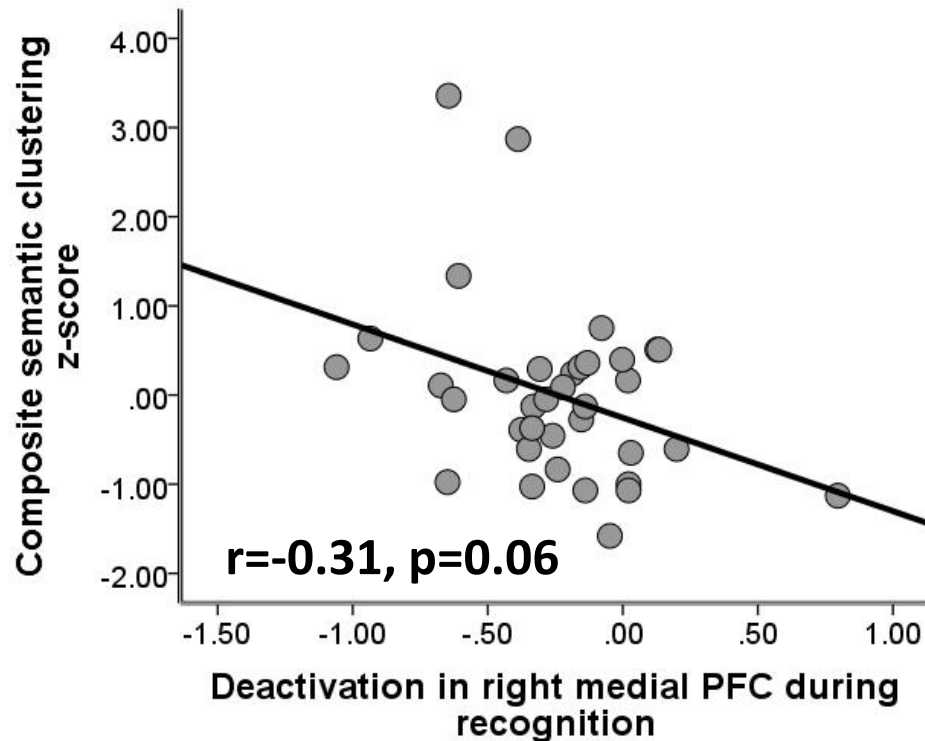
- Activation of bilateral VLPFC, DLPFC, hippocampus, supplementary motor area, motor area, occipital vision regions
- Deactivation of the default mode network

Note. Recognition of novel words (experimental condition) minus repeated recognition of the same two words (control condition),  $p < 0.001$ ,  $k \geq 10$ .

# Perceived stress is associated with lower activation in prefrontal cortex during recognition of words in HIV-infected women



# Greater deactivation in the right medial PFC correlates with decreased semantic clustering on a standardized verbal memory test

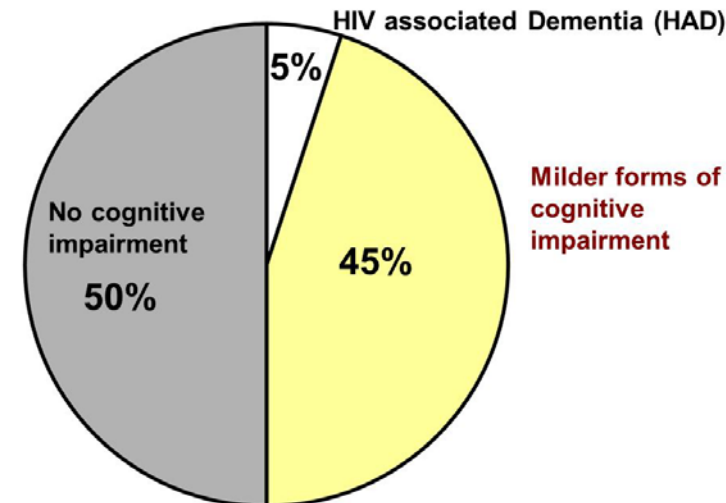


Note. Same pattern seen for HVLT trial 1 cluster score and deactivation in the right medial PFC during recognition,  $r=-0.32, p=0.06$ . Pattern of associations remain the same after controlling for age and recent cd4 count.

# Conclusions

- Stress-related verbal memory deficits, particularly with less efficient strategic encoding in midlife HIV-infected women, may be partially accounted for by alterations in prefrontal cortex functioning
- Understanding the role of the prefrontal cortex in stress-related memory impairments will be particularly important for women aging in the context of HIV as the prefrontal cortex is also particularly vulnerable to aging.

- *What are the clinical implications?*



# Acknowledgements

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- WIHS participants