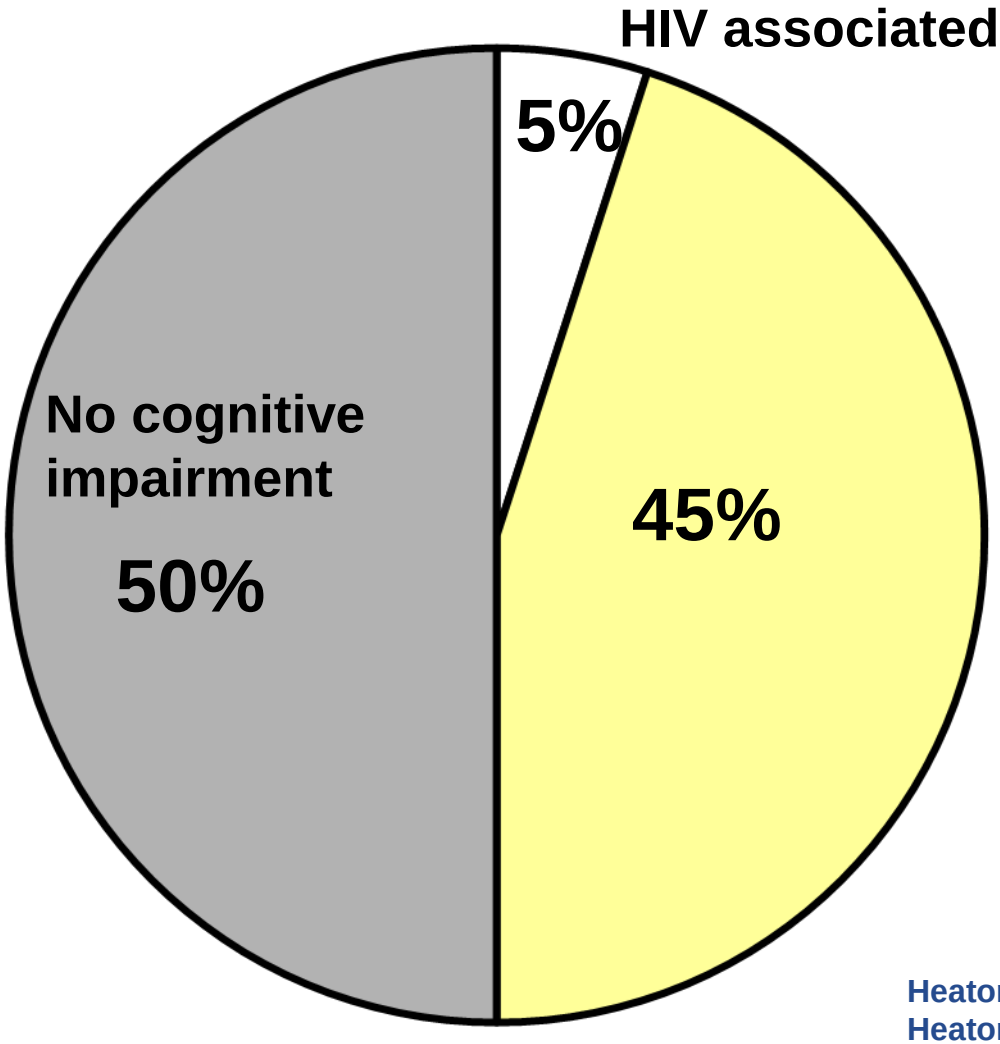
Cognitive aging in the era of effective antiretrovirals

Leah H. Rubin, PhD, MPH
Associate Professor of Neurology & Epidemiology

SETTING THE STAGE

Cognitive dysfunction persists among HIV+ individuals in the era of effective antiretroviral therapies



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

ASSESSMENT

Neuropsychological Testing

Domain	Test
Memory/Learning	Hopkins Verbal Learning Test (HVLT)
Attention	Trail Making Test Part A Letter-Number Sequence Test (LNS; Control Condition)
Working Memory	Letter-Number Span Task (LNS; Experimental Condition)
Executive Function	Stroop Test Trial 3 (read word; inhibit color) **blue, red, green** Trail Making Test Part B
Processing speed	Symbol Digit Modalities Test; Stroop Test Trial 2 (read) words **red, blue**
Fluency	Controlled Oral Word Association Test (COWAT) Semantic Fluency
Motor Skills	Grooved Pegboard

Verbal learning and memory

Broom

Ham

Pencil

Chicken

Notebook

Sponge

Turkey

Detergent

Scissors

Hamburger

Bleach

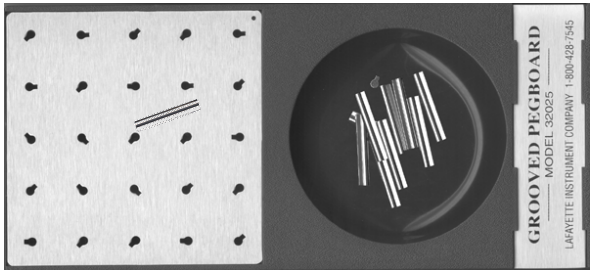
Eraser

Neuropsychological Testing

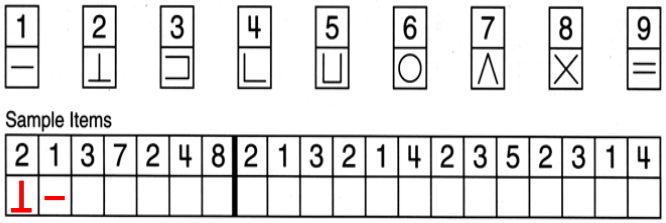
Fluency

little, lily, light, lark,
list, lime, low

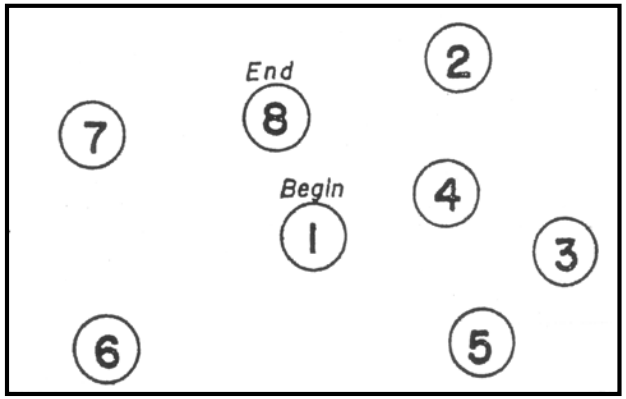
Fine Motor Skills



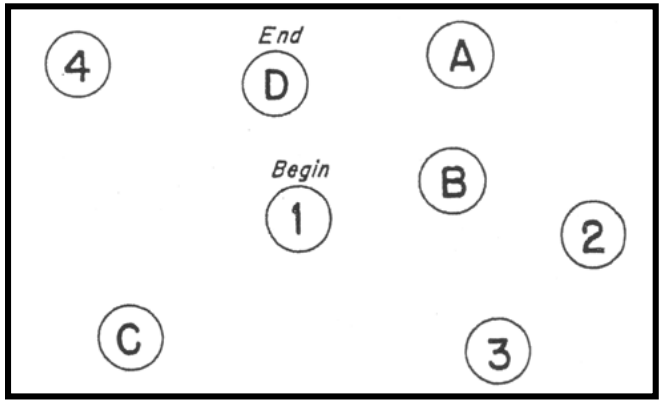
Digit Symbols



Trail Making Test Part A

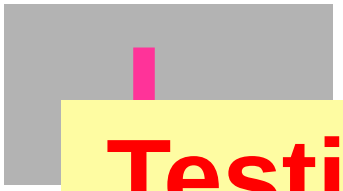


Trail Making Test Part B



Neuropsychological Testing

Fluency

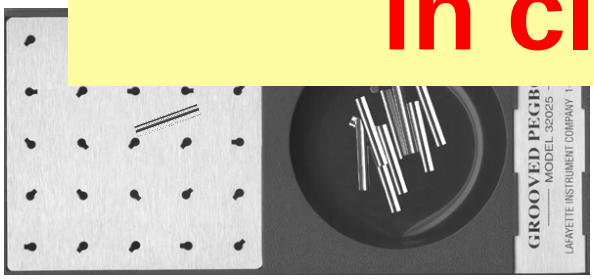


little, lily, light, lark,

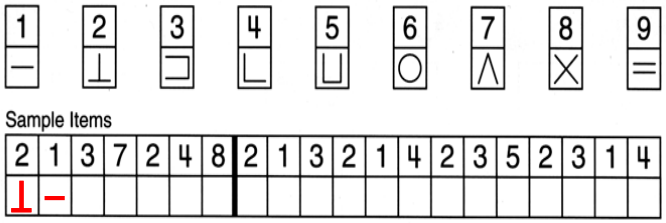
Trail Making Test Part A

Testing is resource intensive in clinical settings

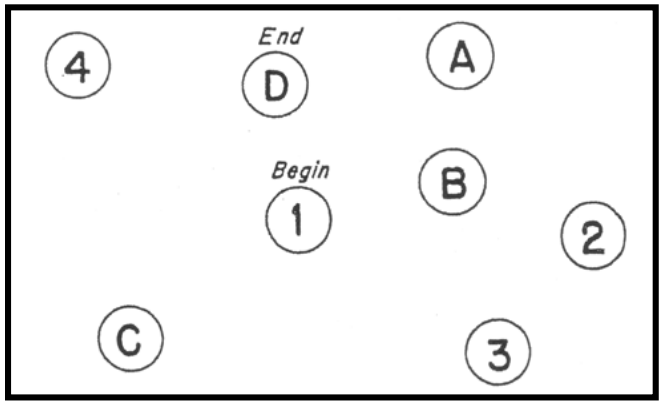
Fine



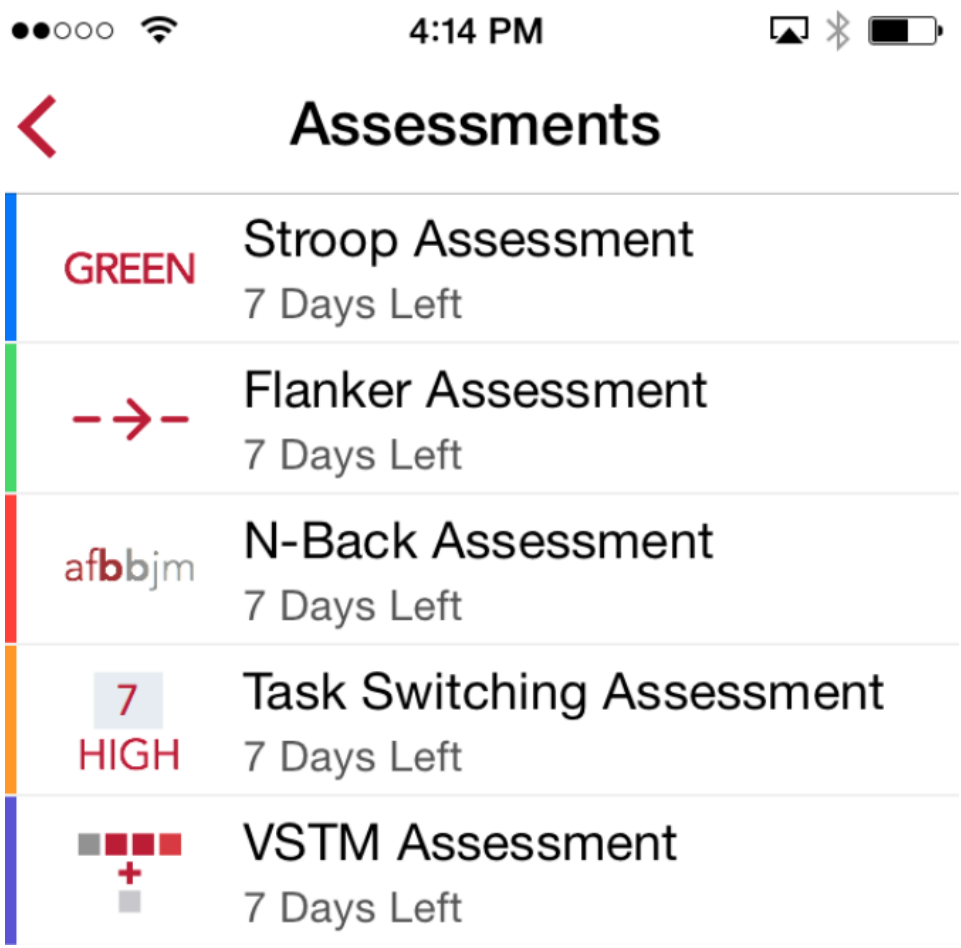
Digit Symbols



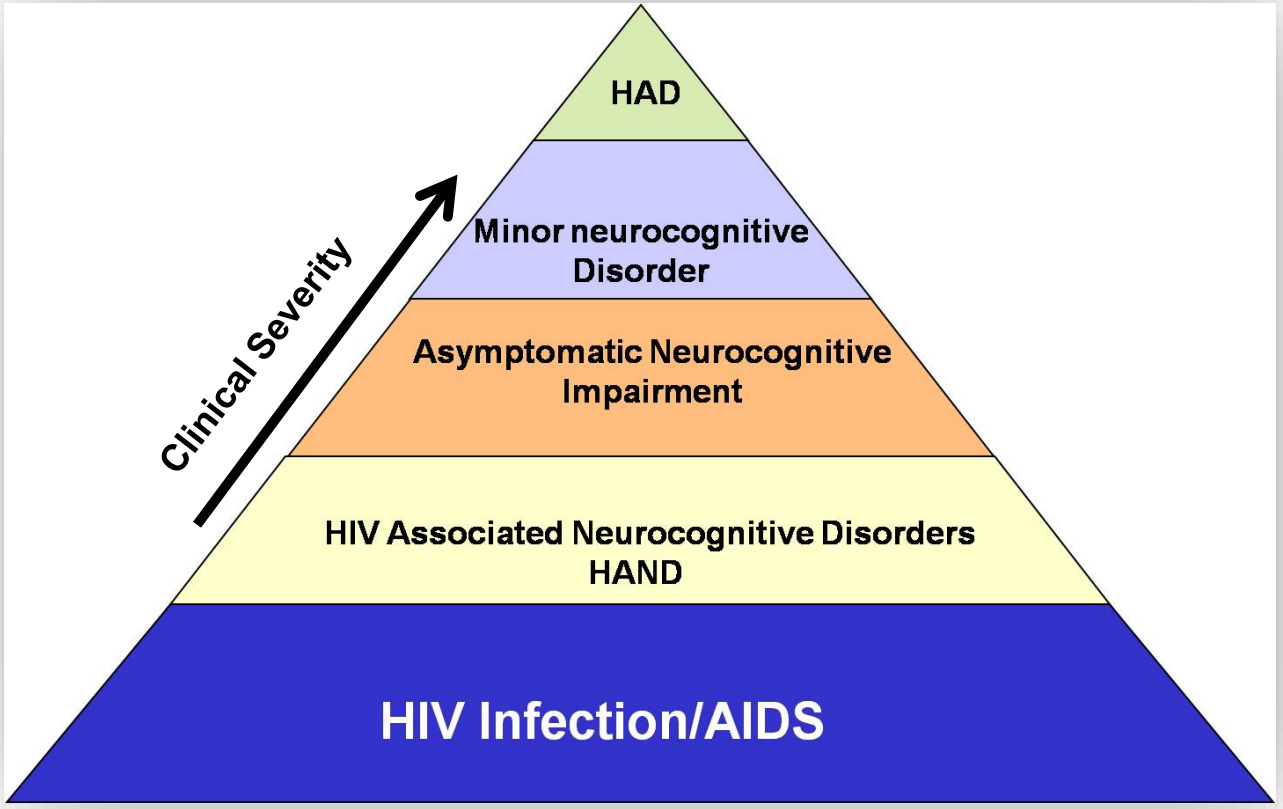
Trail Making Test Part B



Mobile Devices (i.e., apps, tablets)



HIV-associated neurocognitive disorders (HAND)

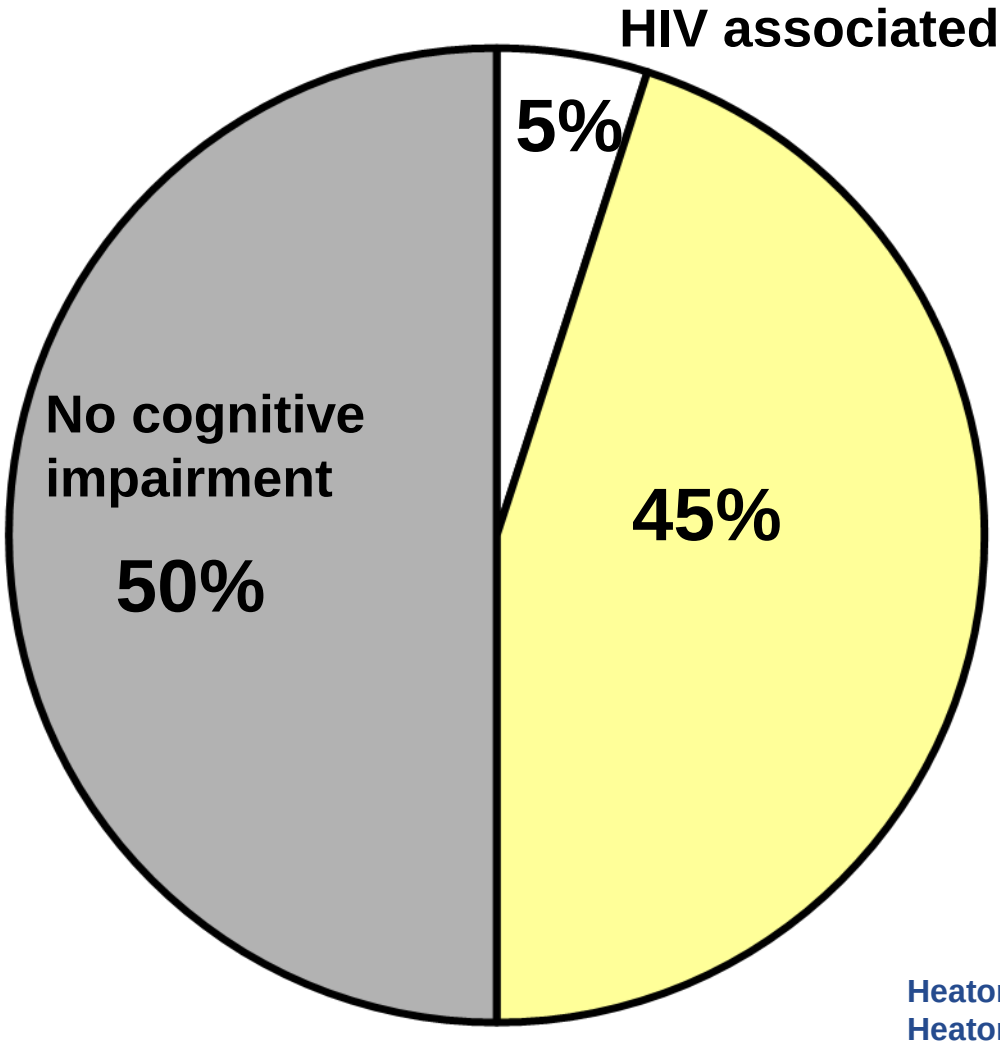


Modified from JC McArthur, MBBS, MPH, at 13th Annual Ryan White HIV/AIDS Program Clinical Conference, IAS-USA

JOHNS HOPKINS MEDICINE

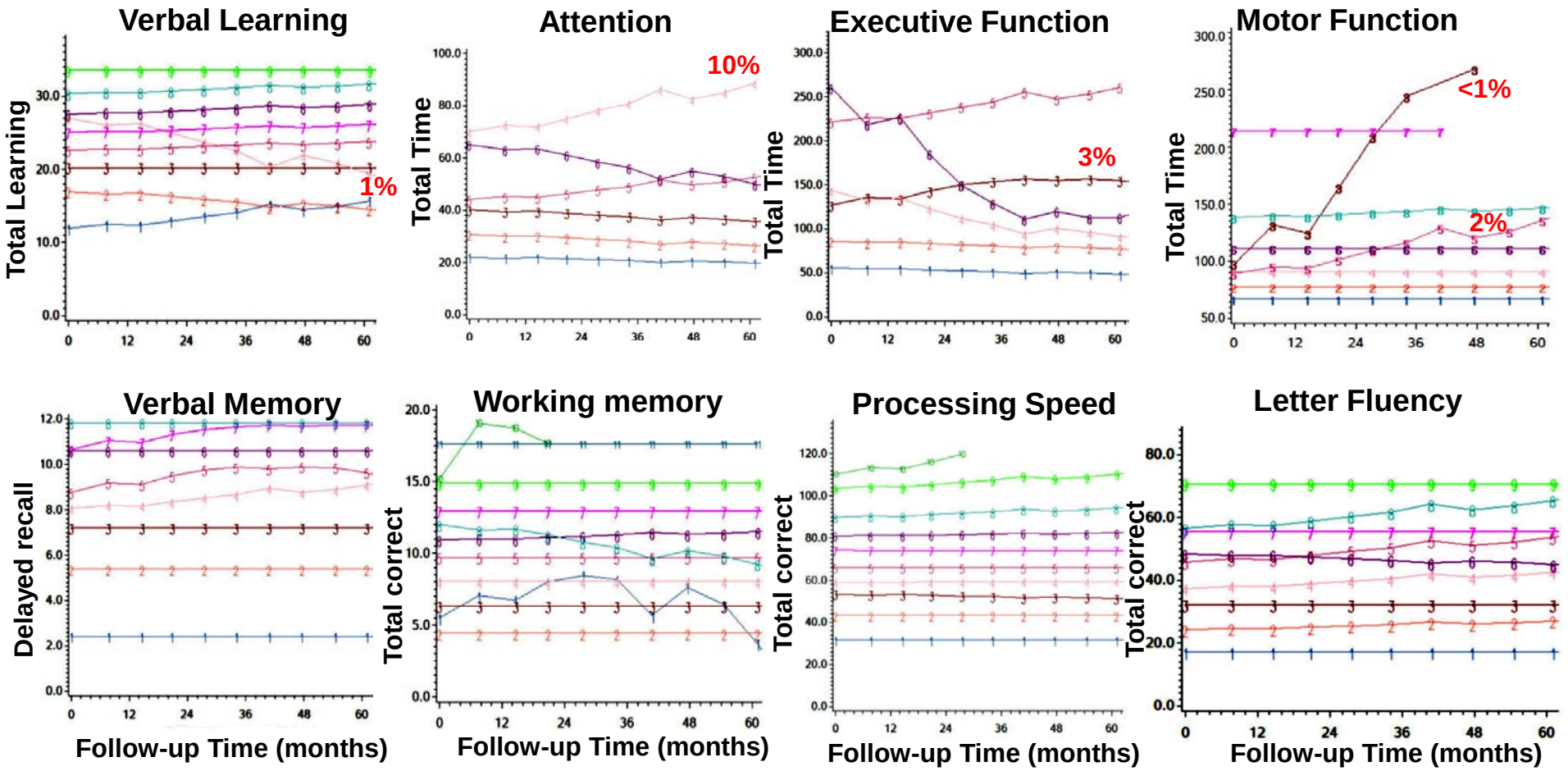
PATTERNS

Cognitive dysfunction persists among HIV+ individuals in the era of effective antiretroviral therapies



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

Cognitive aging in HIV: Heterogeneity is the rule not the exception



N=701; mean age at initial visit ~45yrs; *each outcome modelled separately using group based trajectory analysis; 16% declined on ≥1 test

Brouillette et al. *PLoS One* (2016)

Most studies on HIV-associated cognitive aging includes or focuses on….

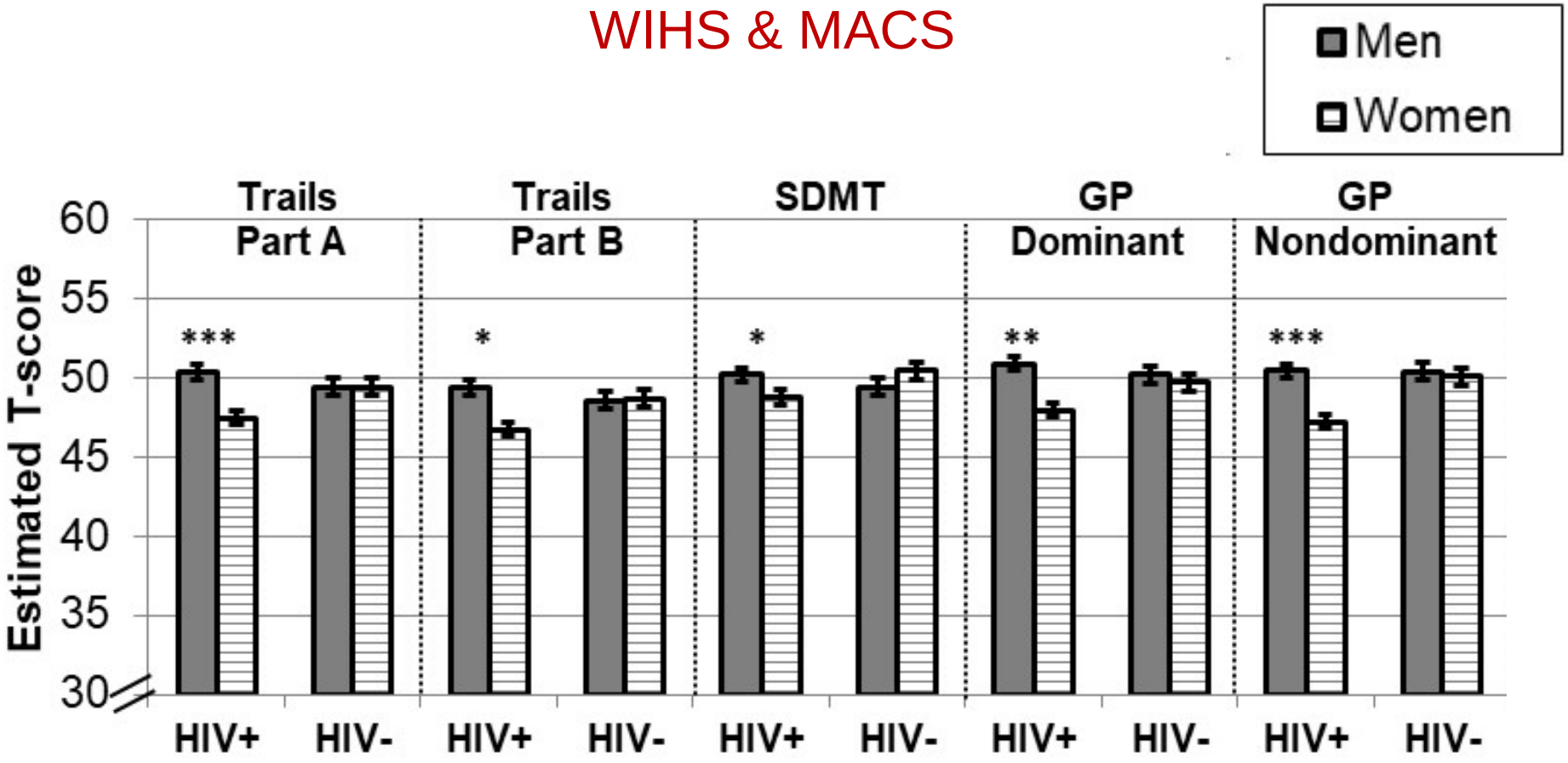
- All or predominantly men living with HIV
- Mixed samples of virological suppressed & unsuppressed individuals
- Global measure of impairment (e.g., HAND)

Heterogeneity

- *Optimize cognitive phenotyping to improve*:
  - understanding of functional consequences
  - identifying underlying pathophysiology, &
  - developing more targeted interventions

Women living with HIV may be more cognitively vulnerable than men living with HIV

WIHS & MACS

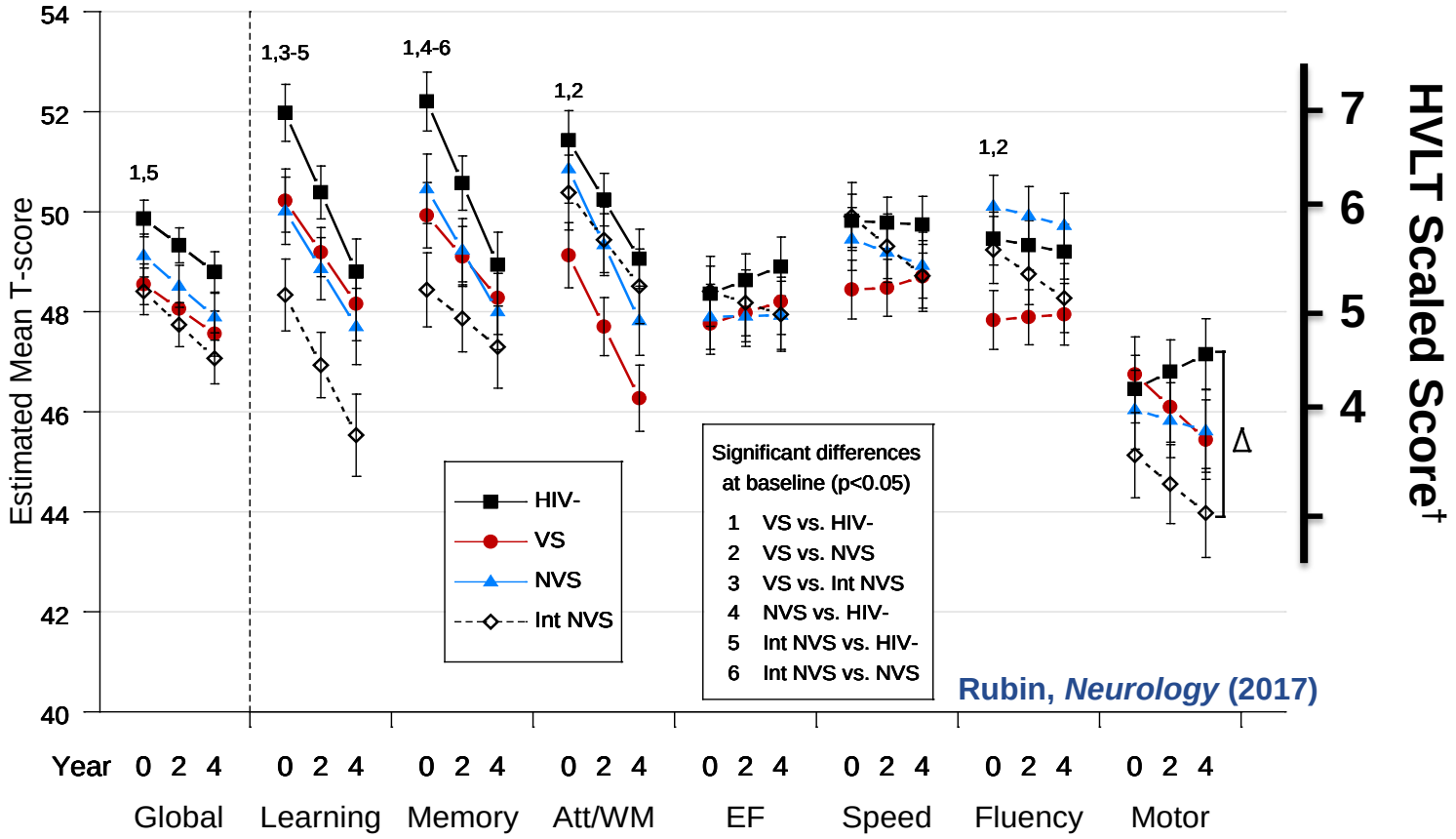


858 HIV+ (429 women)
562 HIV- (281 women)

SDMT=Symbol Digit Modalities test;
GP=Grooved Pegboard

Maki, Rubin, et al. *JAIDS* (2018)

Cognitive impairment persists among virally suppressed women aging with HIV



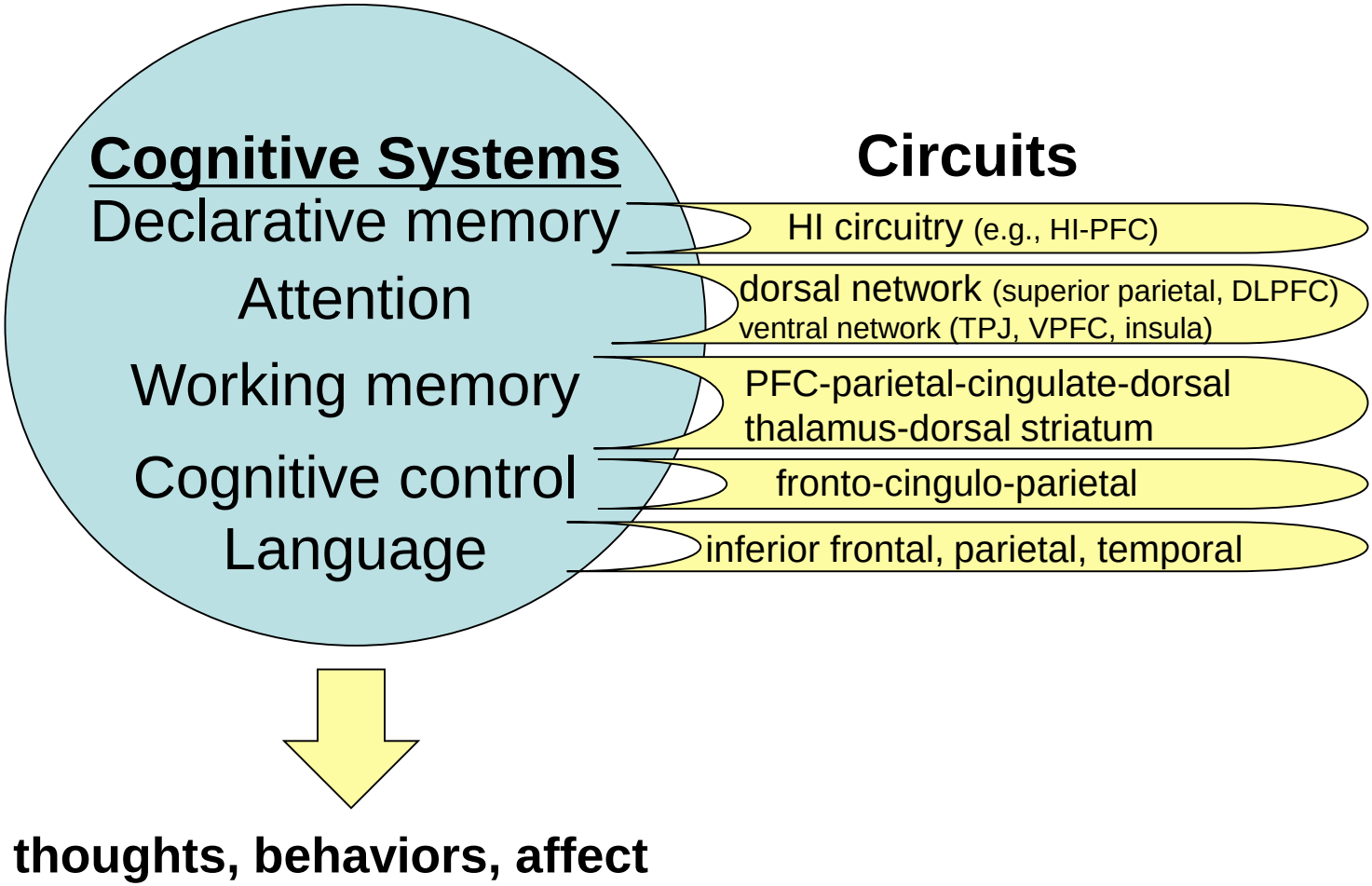
Att/WM=attention/working memory; EF=executive function; VS=consistent use of cART & virally suppressed; NVS=consistent use of cART but inconsistent plasma viral suppression; Int NVS=intermittent cART use & inconsistent plasma viral suppression NVS=not virally suppressed; † Norman, *J Clin Exp Neuropsychol*, (2011); ***p<0.001; **p<0.01; p<0.05; Δ=group difference in slopes at p<0.05

PATTERNS

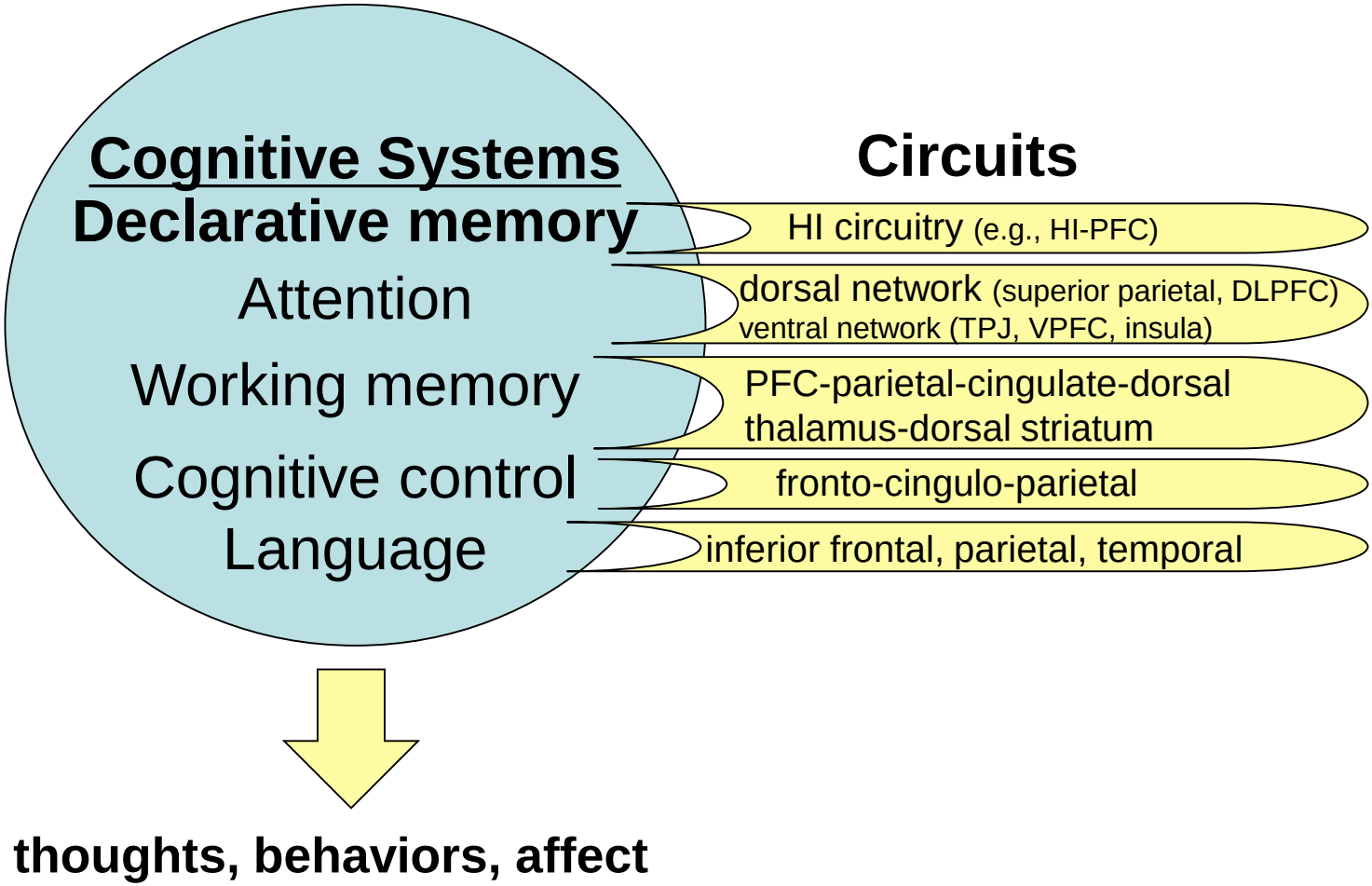
- Heterogeneity in cognitive aging is the rule not the exception
- Women living with HIV may be more cognitively vulnerable than men living with HIV
- Cognitive impairment persists despite continued viral suppression

MECHANISMS

Cognitive systems impacted by aging with HIV



Cognitive systems impacted by aging with HIV

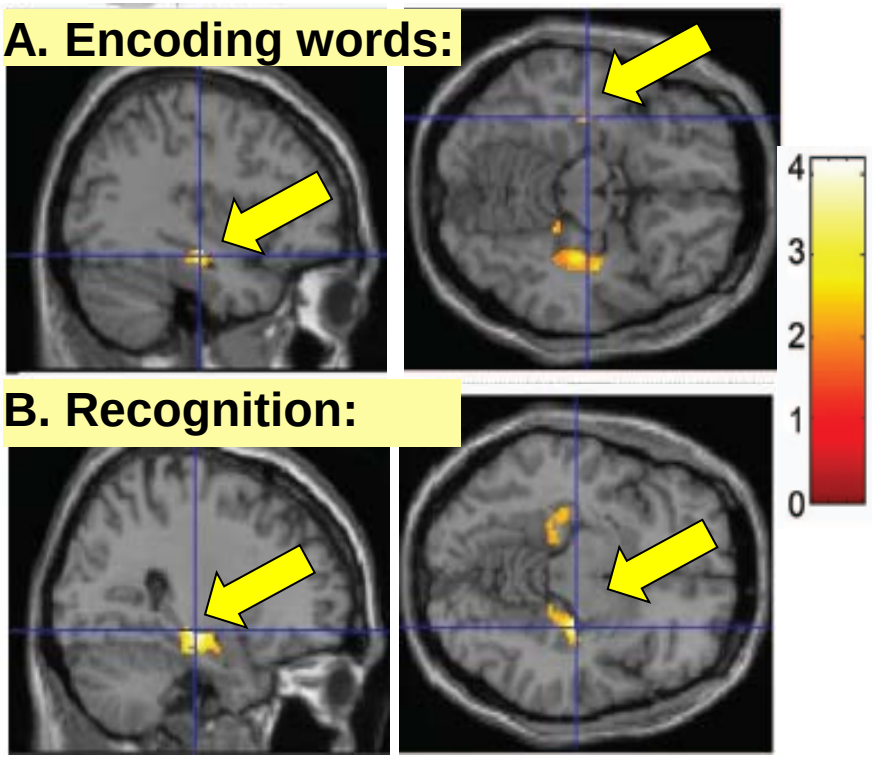


HIV-related alterations in brain function during a declarative memory task in midlife women

Region of interest analysis:

A. Encoding words:

B. Recognition:



↓ HI activity in HIV+ vs. HIV- women

↓ HI activity associated with ↓ HVLT performance (r's>0.54)

↑ HI activity in HIV+ vs. HIV- women

↑ HI activity associated with ↓ HVLT performance (r's<-0.62)

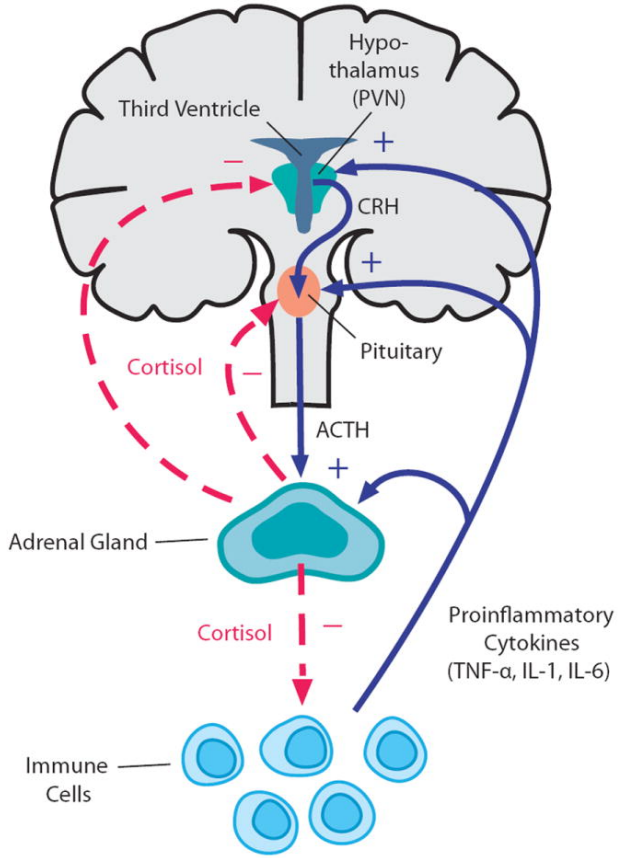
Whole-brain analysis: **HIV-alterations in PFC during encoding & recognition; PFC related to ↓ HVLT performance**

Maki, Rubin et al., *Neurology* (2009)

Hormonal and inflammatory contributions to declarative memory dysfunction in virally suppressed midlife HIV+ women

Mechanisms

Hormonal & inflammatory



Silverman et al., *Annals of the NYAS* (2012)

Cognitive System

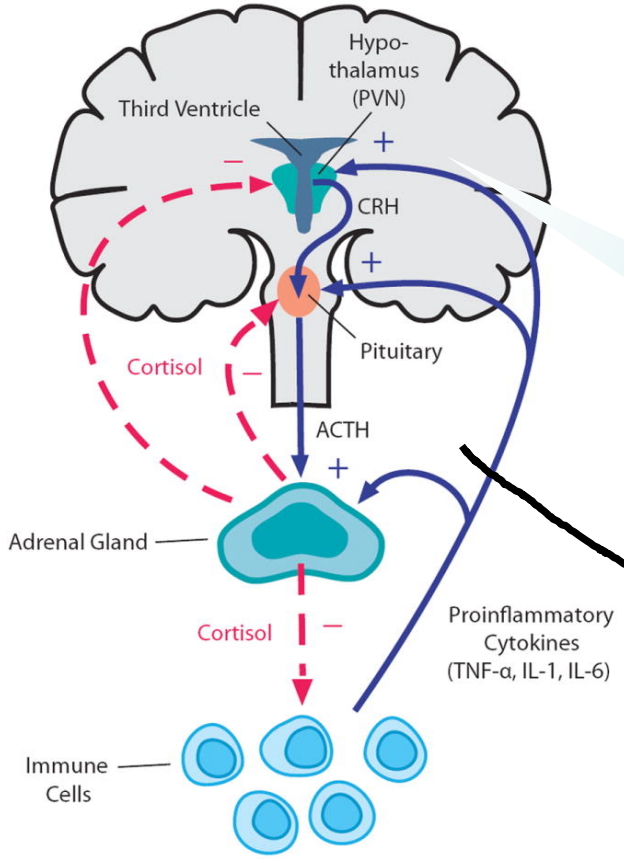
Declarative Memory

Circuits

HI circuitry (e.g., HI-PFC)

Hormonal and inflammatory contributions to declarative memory dysfunction in virally suppressed midlife HIV+ women

Mechanisms
Hormonal & inflammatory



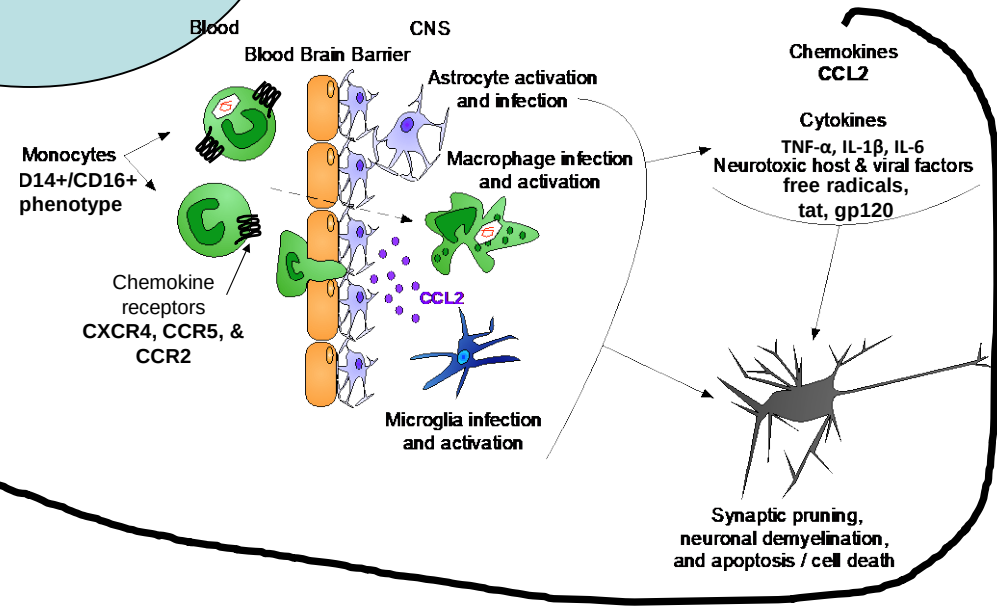
Silverman et al., *Annals of the NYAS* (2012)

Cognitive System

Declarative Memory

Circuits

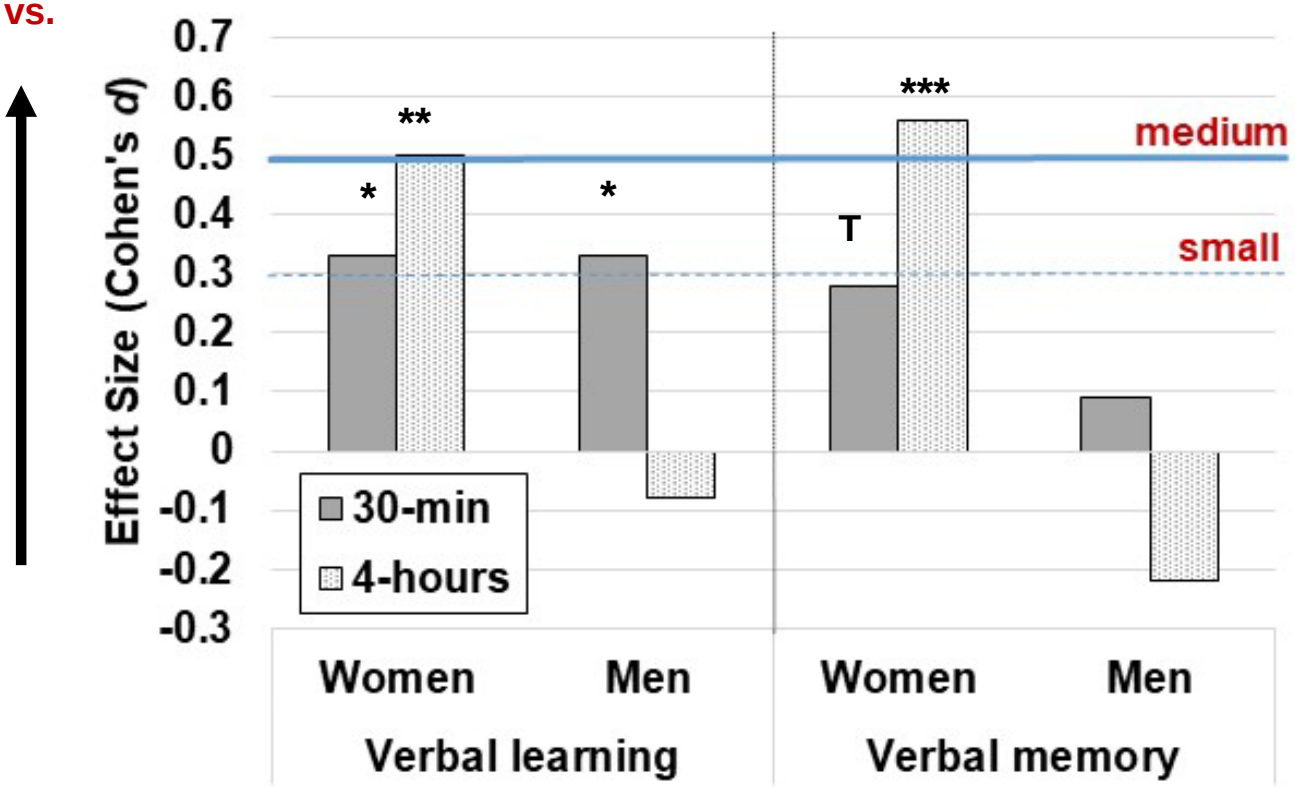
HI circuitry (e.g., HI-PFC)



Slide courtesy of Dr. Joan Berman
Adapted from: Williams & Veenstra, et al, 2014

Probing the HPA axis & inflammation using low dose hydrocortisone (LDH) improves learning & memory at the 4-hour time point in HIV

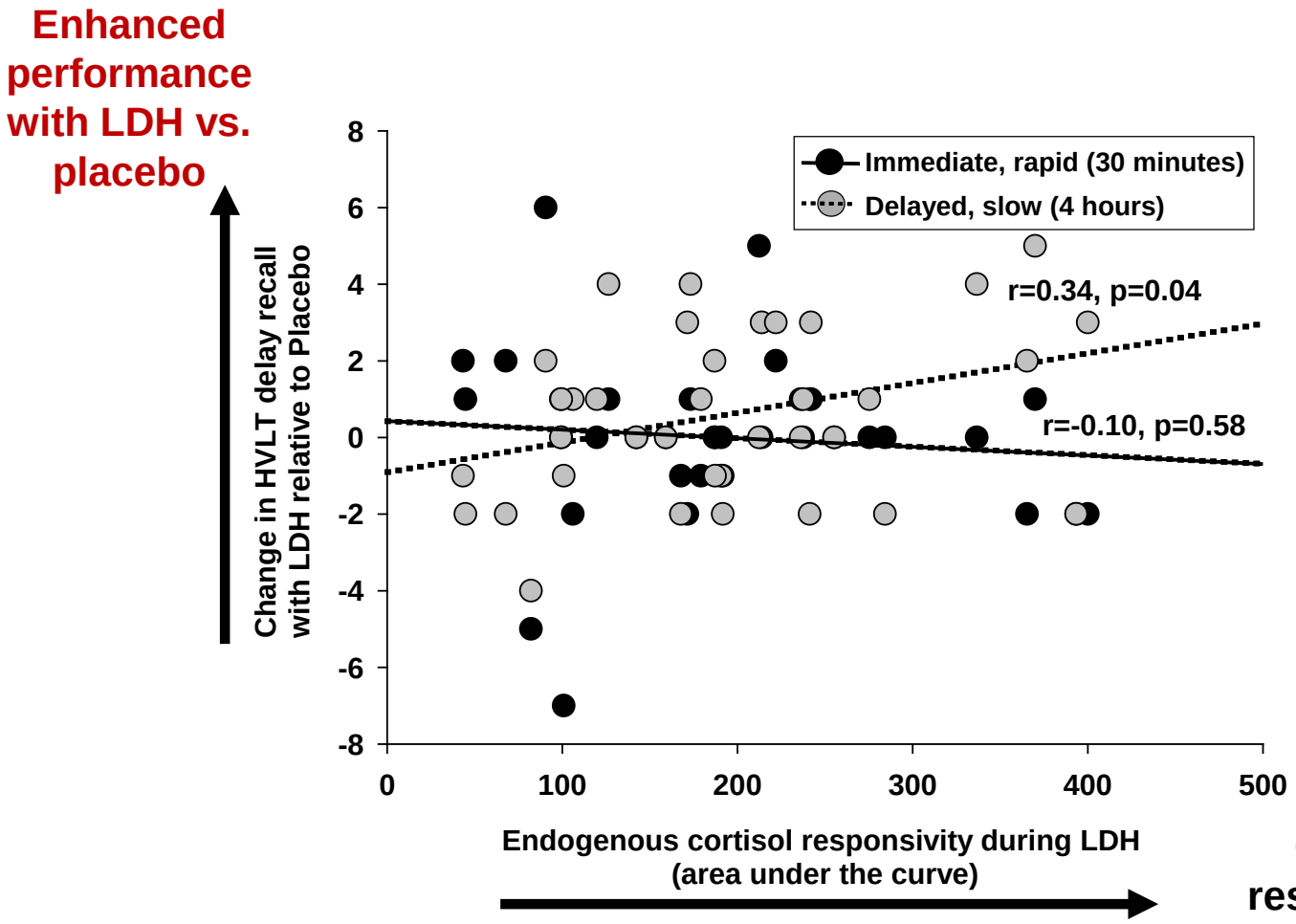
LDH improves performance vs. placebo



***p<0.001; **p<0.01; *p<0.05; ^{T}=0.06.

Rubin, *JAIDS* (2017);
Rubin, *AIDS* (2018)

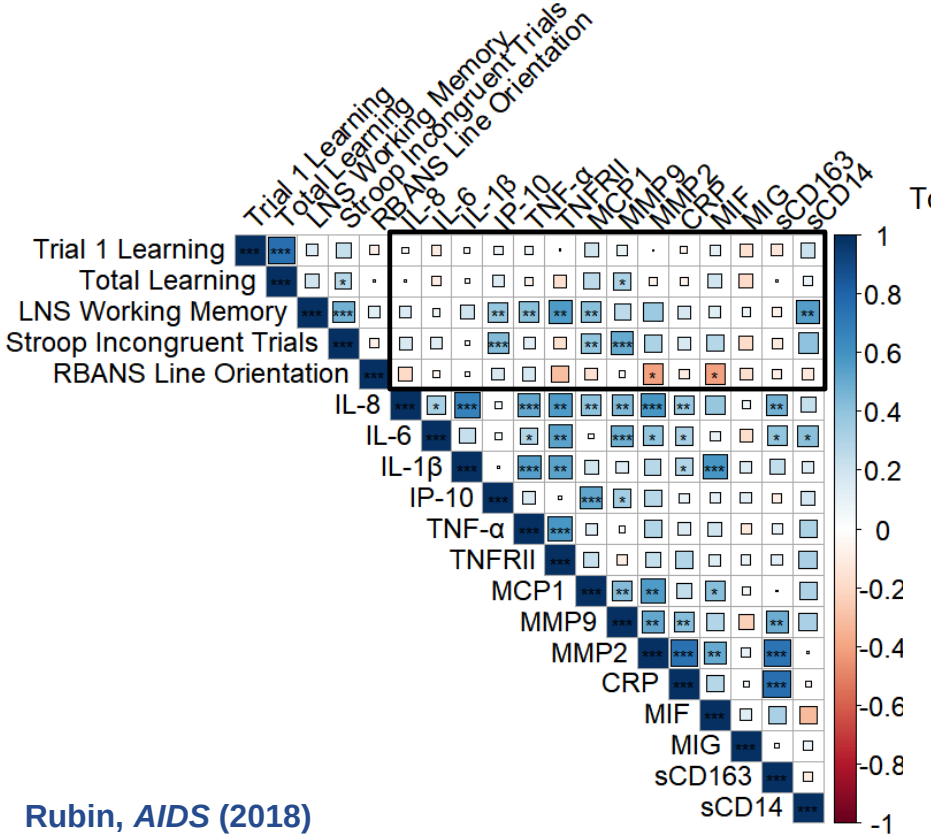
Magnitude of increase in salivary cortisol responsivity due to low dose hydrocortisone (LDH) is associated with verbal memory improvement at the 4 hour time point



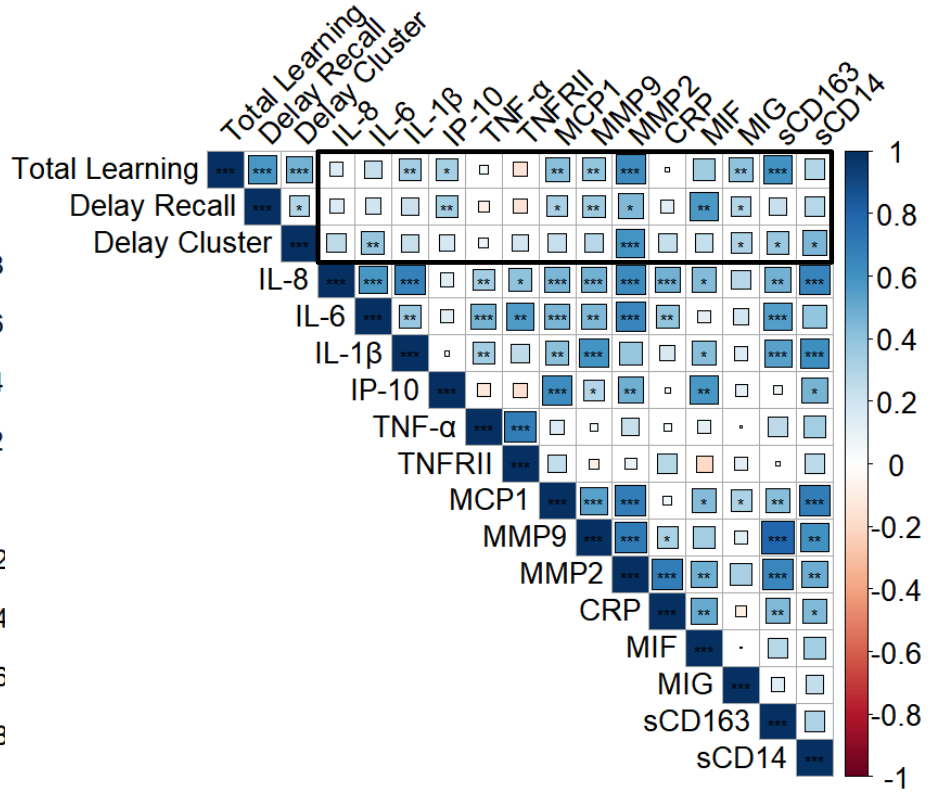
Rubin, *JAIDS* (2017);
Rubin, *AIDS* (2018)

Degree to which LDH suppresses inflammatory activity is associated with LDH improvements in learning and memory only in HIV+ women

Immediate, rapid (30 min)



Delayed, slow (4 hours)



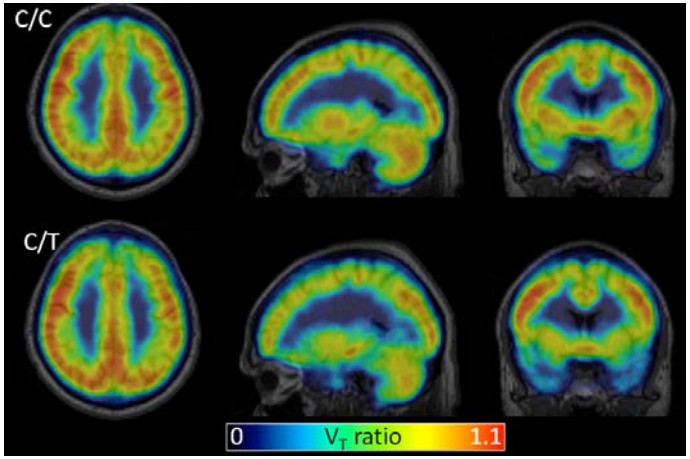
Rubin, *AIDS* (2018)

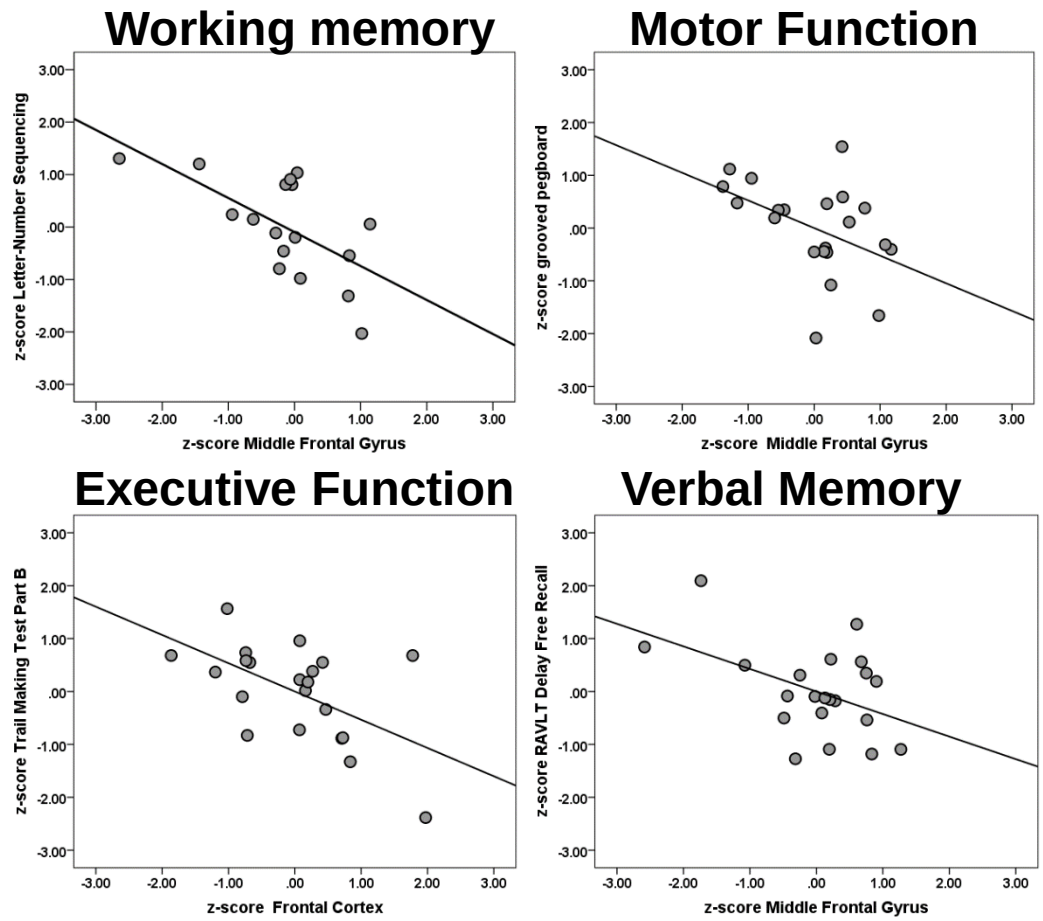
*****p<0.01; **p<0.05; *p<0.10; immune responsivity = placebo – LDH ; cognitive improvement = LDH – placebo; Positive association (blue) = greater inflammatory reduction; greater cognitive improvement**

Higher region-specific microglial activation in the frontal cortex is associated with lower cognition in HIV+ virally suppressed individuals

Using [^{11}C]DPA-713 with positron emission tomography (PET) to image translocator protein 18 KDa (TSPO), a marker of microglial activation

Mean binding of the radiotracer

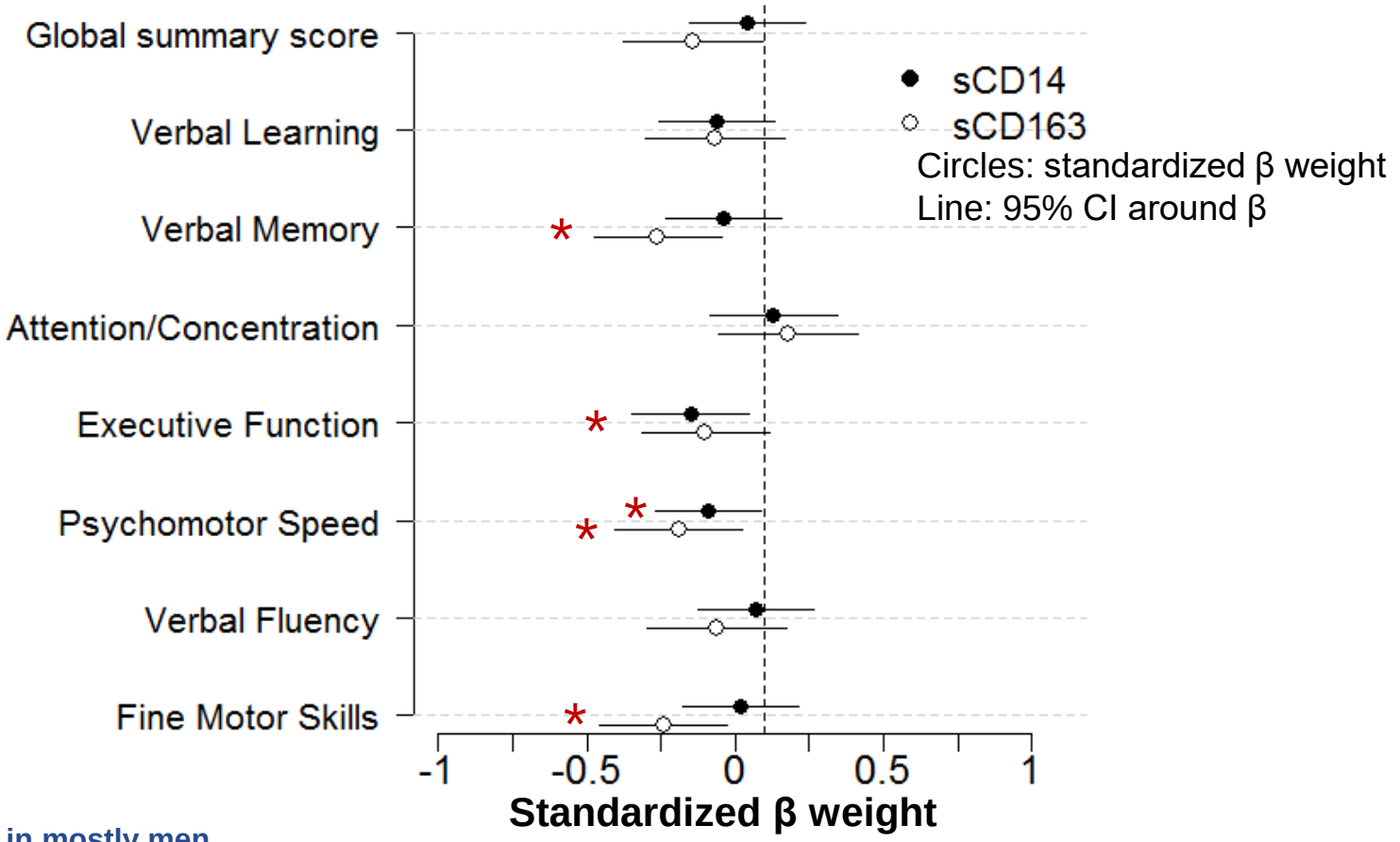




Rubin, Sacktor, Coughlin et al., AIDS (in press)

Higher monocyte-driven inflammation predicts lower cognitive performance in midlife HIV+ virally suppressed women

Soluble markers of myeloid-specific activation (sCD14, sCD163)



See for similar findings in mostly men
Burdo et al., *AIDS (2013)*—global, learning, executive function
Royal et al., *PLoS One* (2016)—global in women only

Imp, Rubin, Valcour et al., *J Infect Dis* (2016)

MECHANISMS

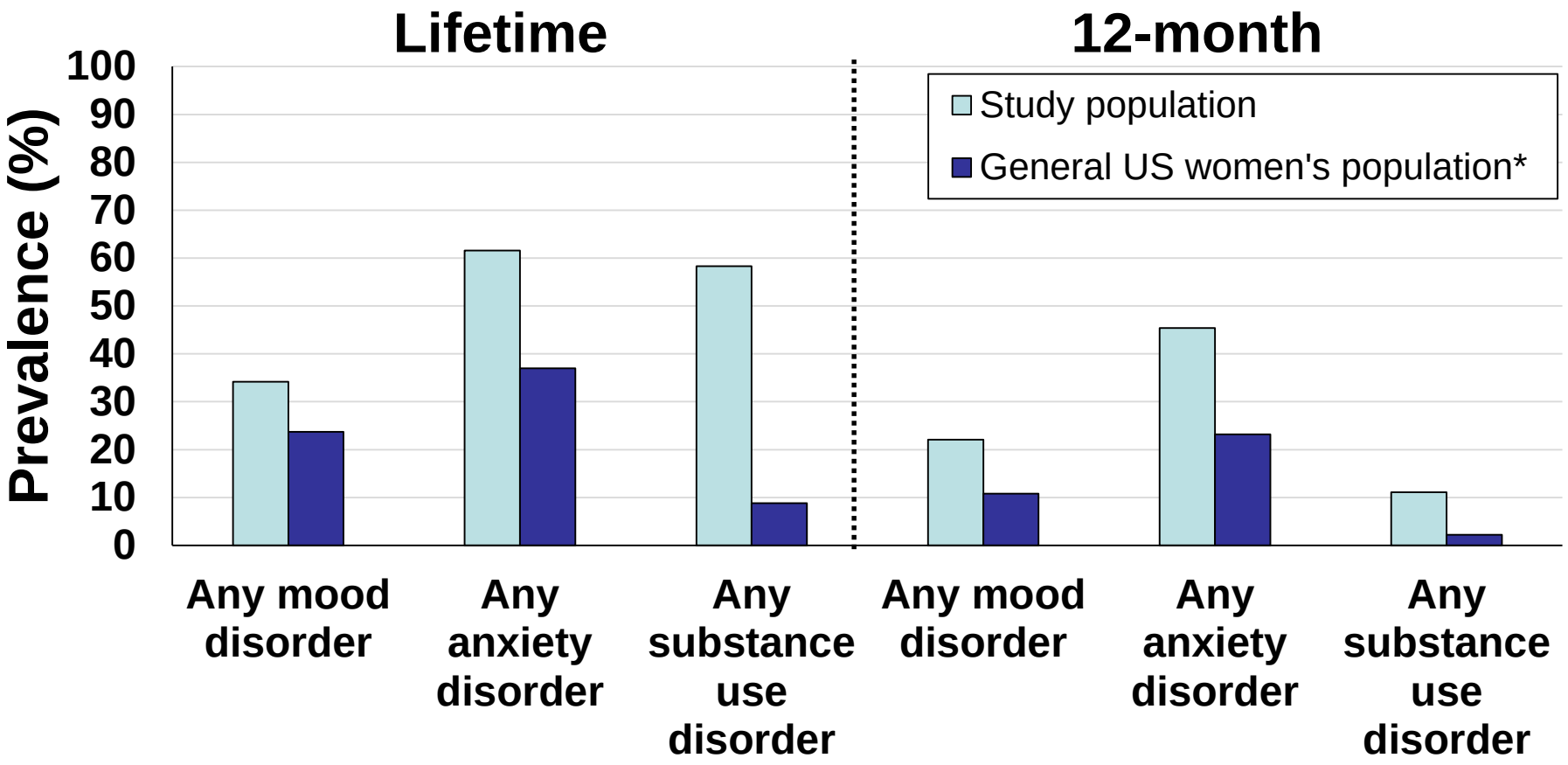
- Alterations in prefrontal-limbic function subserve the declarative memory deficit in midlife virally suppressed individuals
- HPA axis and inflammation may be a potential mechanisms driving cognitive deficits in learning/memory

PREDICTORS

PREDICTORS

- Mental Health

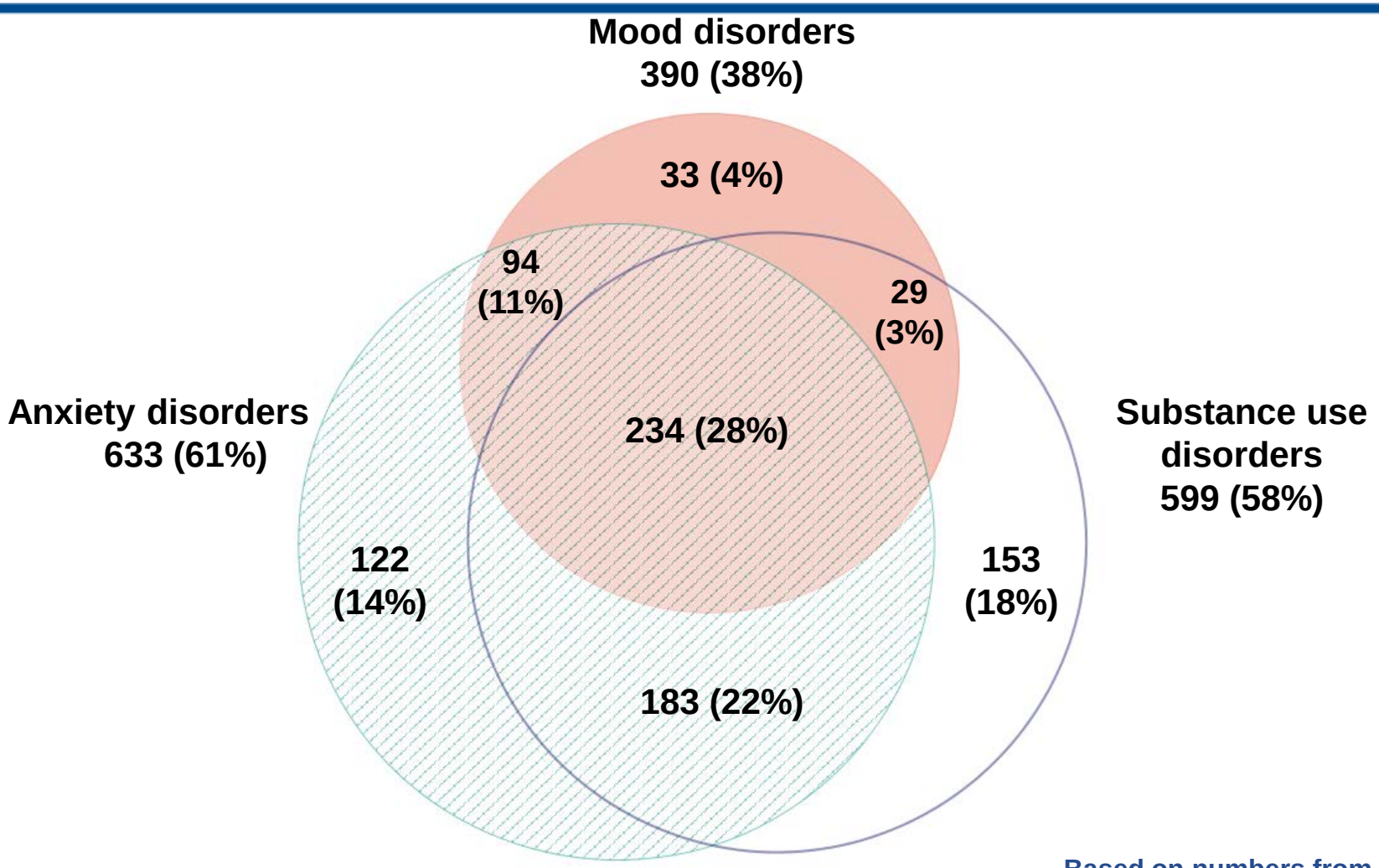
Prevalence of mental health disorders among 1027 WIHS midlife women living with HIV



CIDI=Composite International Diagnostic Interview
* National Comorbidity Survey Replication (NCS-R)

Cook, et al. *AIDS* (2018)

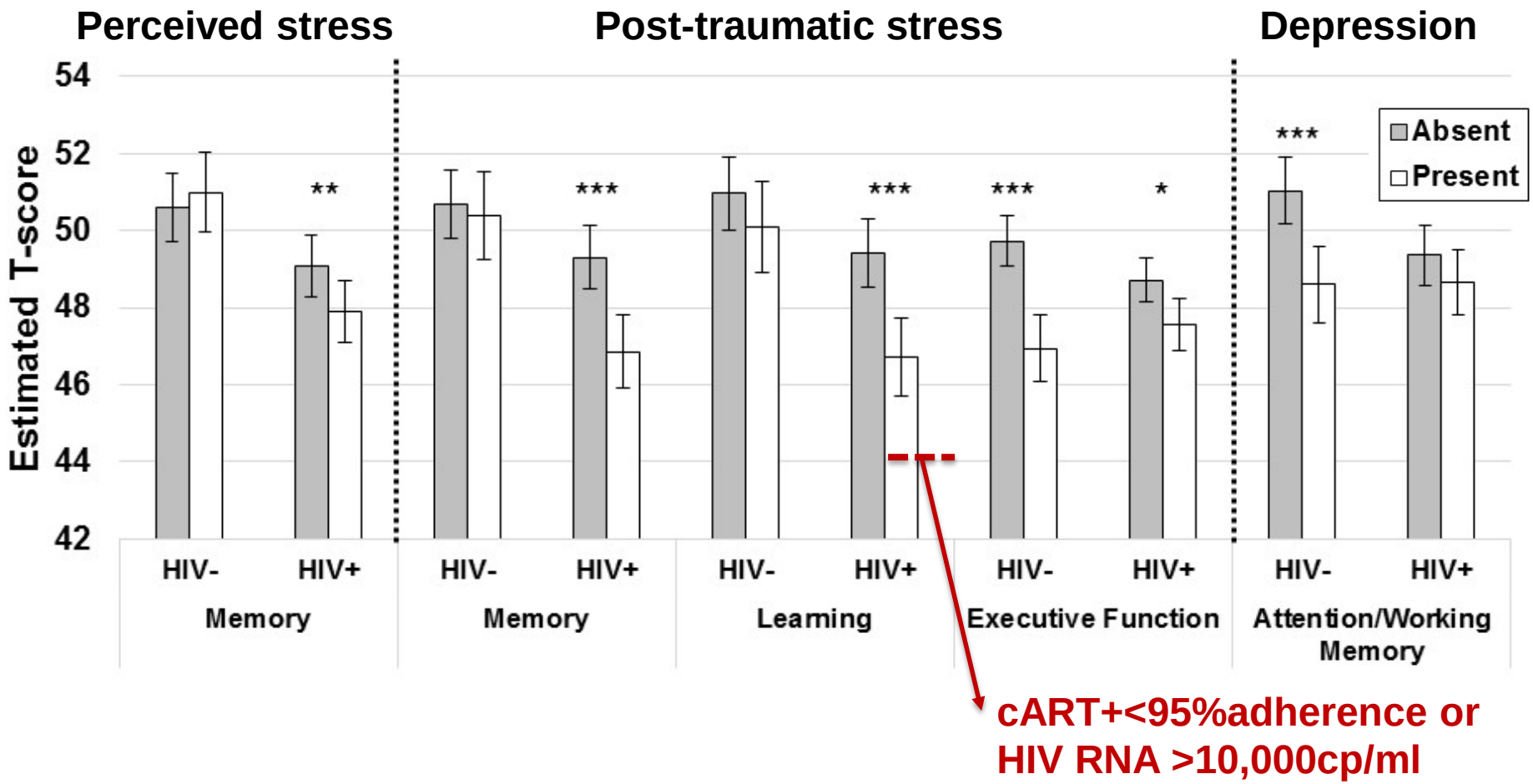
Lifetime mental health comorbidities among 1027 WIHS midlife women living with HIV



CIDI=Composite International Diagnostic Interview

Based on numbers from Cook, et al. *AIDS* (2018)

Perceived and post-traumatic stress are associated with decreased cognition in midlife HIV+ women

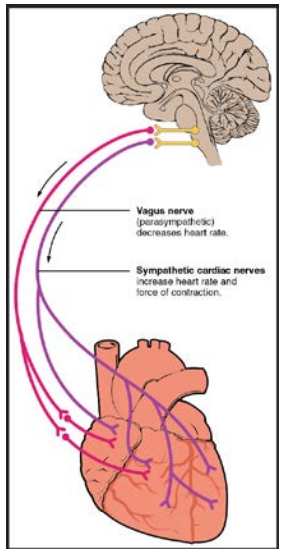


***p<0.001; **p<0.01; *p<0.05

Rubin et al., *AIDS* (2017)

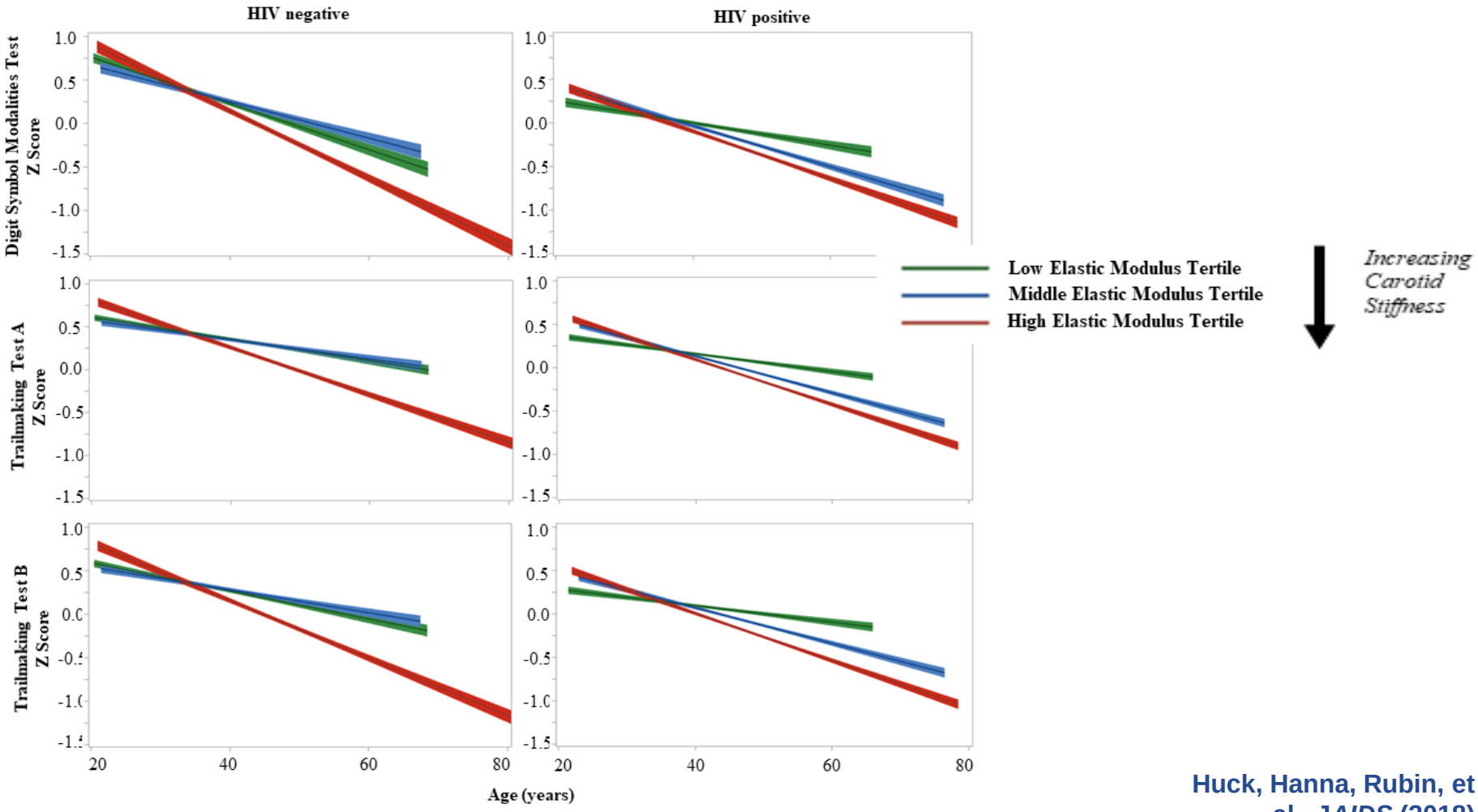
PREDICTORS

- Mental Health
- Cardiovascular risk factors



Researchgate.net

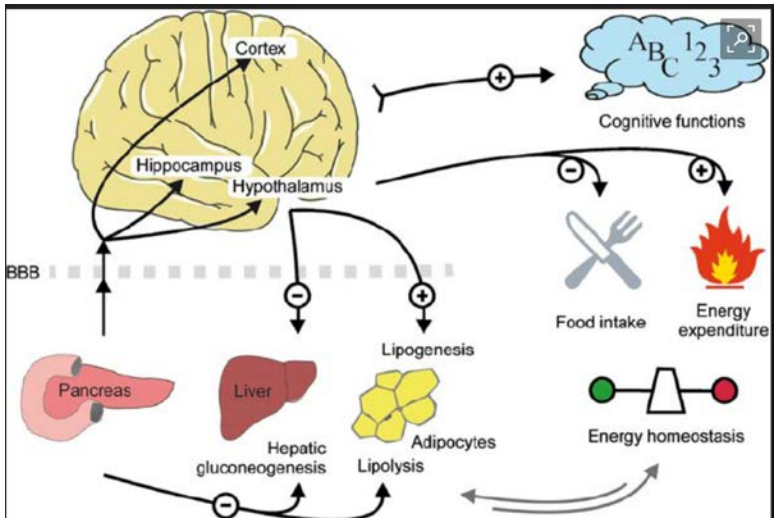
Arterial stiffness is a risk factor for cognitive aging among WIHS women



Huck, Hanna, Rubin, et al., *JAIDS* (2018)

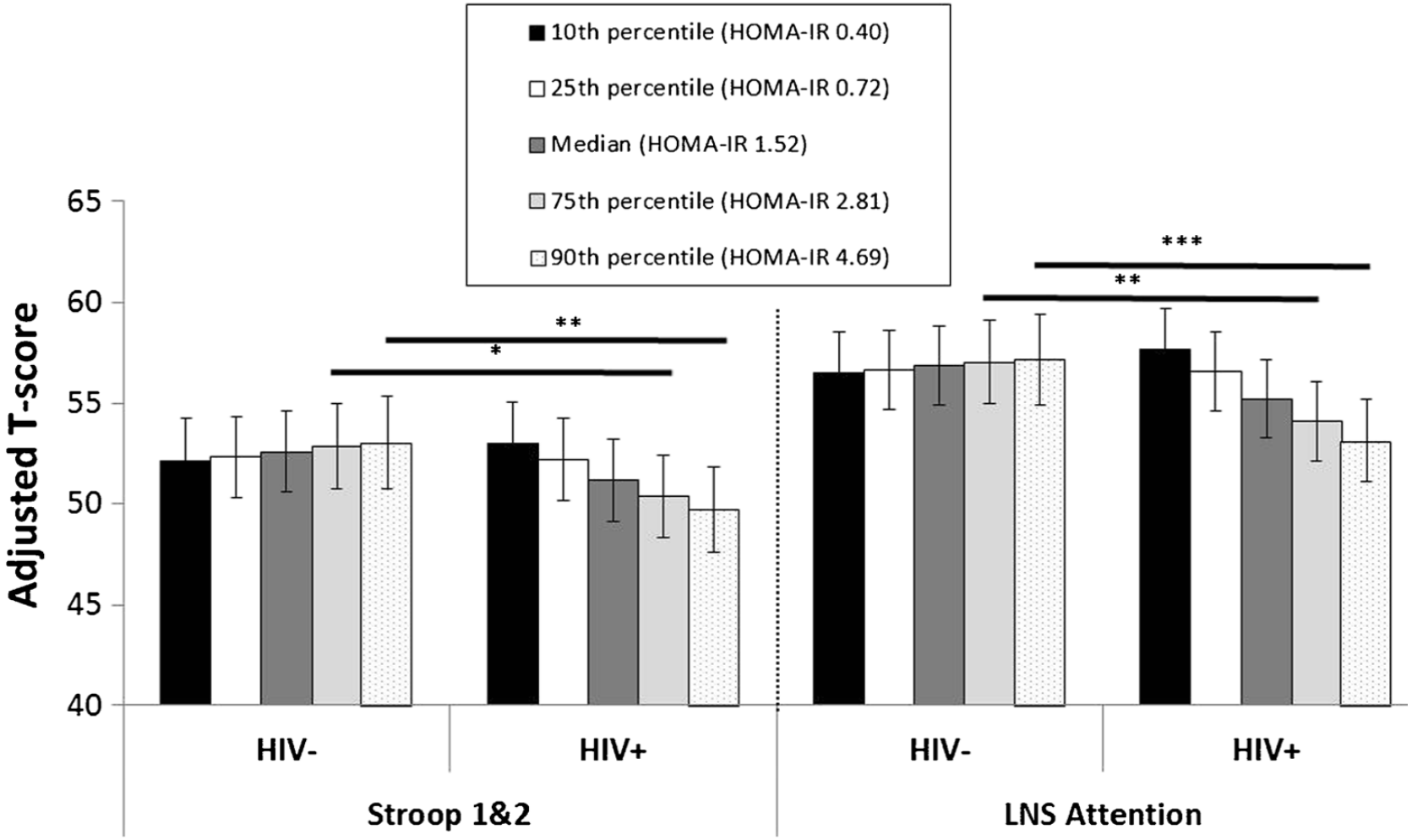
PREDICTORS

- Mental Health
- Cardiovascular risk factors
- Metabolic risk factors



Researchgate.net

HIV modulates the association of insulin resistance and attention among midlife women with HIV

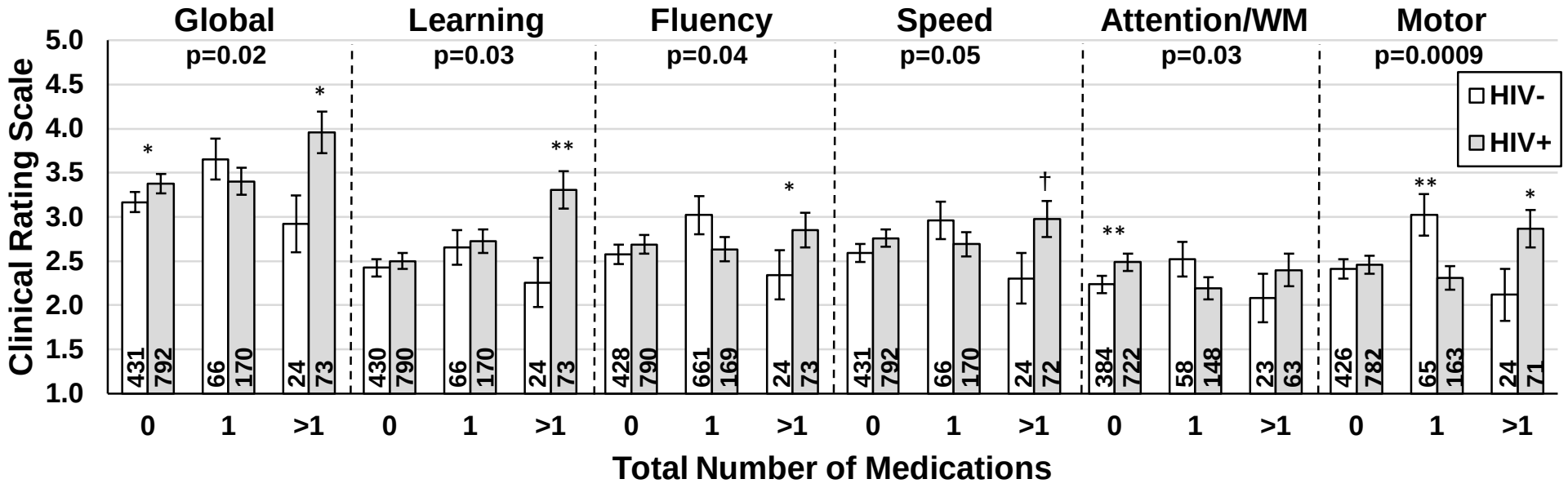


Valcour, Rubin et al., *JNV* (2015)

PREDICTORS

- Mental Health
- Cardiovascular risk factors
- Metabolic risk factors
- Polypharmacy

Cognitive burden of common medications with anticholinergic properties among midlife women with HIV

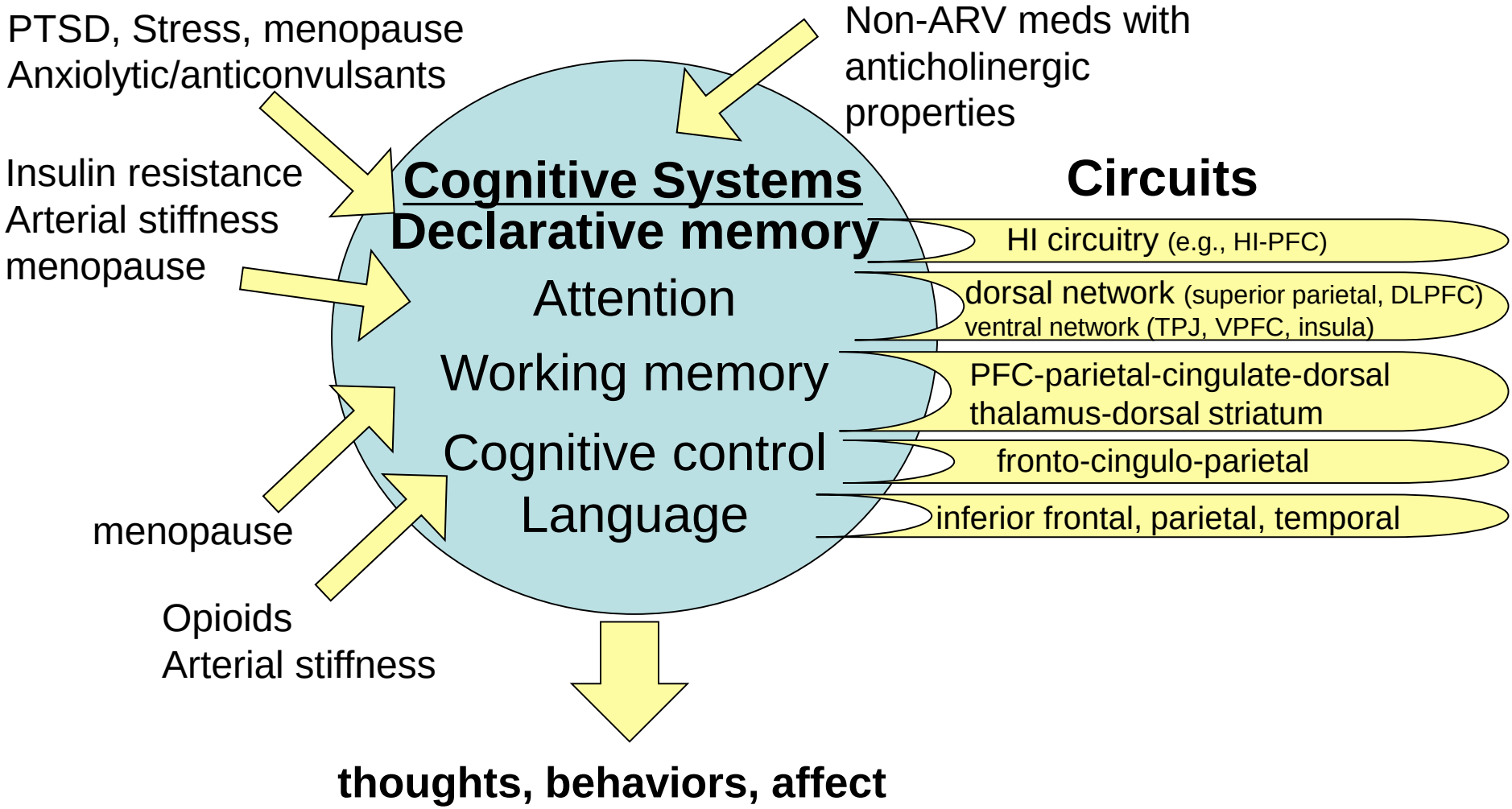


Commonly used medications in WIHS women with anticholinergic properties:
Antidepressants: Trazodone, Paroxetine, Mirtazapine, Amitriptyline
Antipsychotics: Quetiapine, Risperidone, Olanzapine
Muscle relaxants: Baclofen, Cyclobenzaprine
Antihistimine: Loratadine, Diphenhydramine, Hydroxyzine

***p<0.001; **p<0.01; *p<0.05

Rubin, Bishop et al., J*AIDS* (2018)

Cognitive systems impacted by aging with HIV



Summary/Conclusion

- **Assessment:**
  - Standard neuropsychological testing; app/tablet based assessments
  - Are we using the right measures?
- **Patterns**:
  - Persistent cognitive impairment despite viral suppressed in HIV
  - Considerable heterogeneity in cognitive systems impacted with age
- **Mechanisms**: example in midlife women:
  - Alterations in prefrontal-limbic function subserve declarative memory deficit in HIV
  - HPA axis and inflammation may be a potential mechanisms driving some of the mental health+cognitive deficits in declarative memory
  - Treatments targeting alterations might provide cognitive benefit in HIV+ individuals
- **Predictors**:
  - Numerous factors (mental health, cardiovascular, metabolic, polypharmacy) contribute or exacerbate HIV effects on specific cognitive systems

Acknowledgements

University of Illinois at Chicago

- Pauline M. Maki, PhD
- Judith Cook, PhD
- K. Luan Phan, MD

Johns Hopkins University

- Jenn Coughlin, MD
- Ned Sacktor, MD

Women's Interagency HIV Study (WIHS)/Multicenter AIDS Cohort Study (MACS)

- Victor Valcour, MD, PhD (UCSF)
- Eileen Marin, PhD (Rush)
- Deborah Gustafson, PhD (Suny-Downstate Medical Center)
- Ned Sacktor, MD (JHU)
- Todd Brown, MD (JHU)
- Neuropsychology Working Group
- WDMAC (Gayle Springer, Lorie Benning)
- WIHS/MACS participants

Other Collaborators:

- Erin Sundermann, PhD (UCSD)
- Sheila Keating, PhD
- Jeffrey Bishop, PhD (U of Minnesota)

Funding

- Building Interdisciplinary Research Careers in Women's Health Awardee (K12)
- NIMH: K01MH098798 (PI: Rubin)
- NIMH: R21MH099978 (PI: Rubin)
- NIMH: R01MH113512 (PI: Rubin)
- DCFAR pilot grant, UIC CRB pilot grant