

Brain health complications in women with HIV: where do we go from here?

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Brain & Mental Health Scientific Committee

Aims to determine optimal & feasible methods for the prevention & management of co-infections & comorbidities of HIV infection & its treatment.



Priorities include evaluation of:

- ▶ Investigating potential neuroprotective & neurotoxic ART effects to preserve cognitive & mental health development in infants, children, & adolescents
- ▶ Refining & optimizing evaluation & treatment of cognitive & mental health disorders, particularly executive dysfunction, depression & PTSD
- ▶ Evaluating novel preventive & /or therapeutic approaches to high-priority diseases among pediatric populations with or affected by HIV, including respiratory syncytial virus, working with NIAID & other partners
- ▶ Evaluating other co-morbidities & complications of importance for pediatric, adolescent & pregnant populations with HIV, with other partners & NIH

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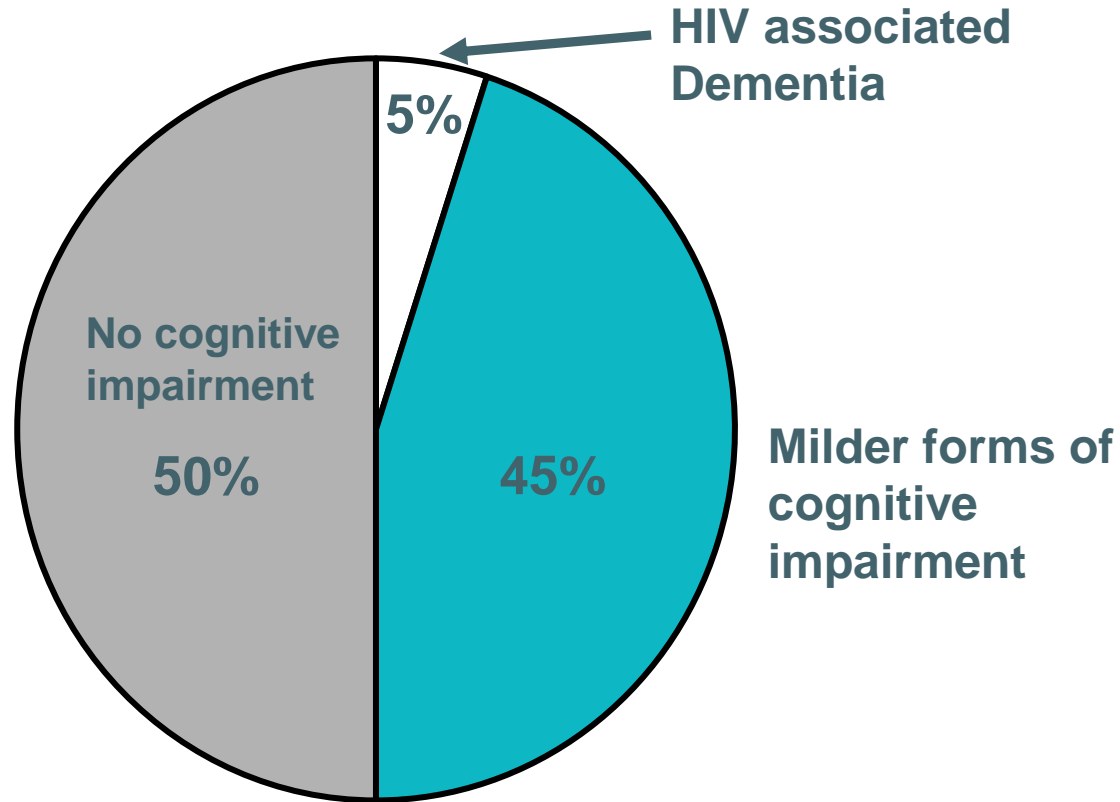
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SETTING THE STAGE

Magnitude of the problem

Cognitive complications persist among people with HIV



Cognitive assessments (endpoints) typically used in neuroHIV studies

Domains	Test
Verbal Learning & memory	Hopkins Verbal Learning Test (HVLT)
Attention/Working memory	Letter-Number Sequence Test
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 Semantic Fluency
Motor Skills	Grooved Pegboard

Mental health complications persist among people with HIV

Condition in past 12 months	% Screening Positive (95% CI)	
	HCSUS* (N=2864)	NHSDA (N=22,181)
Major Depression	36.0 (33.6-38.3)	7.6
Dysthymia	26.5 (23.5-29.5)	-
Generalized Anxiety Disorder	15.8 (14.0-17.7)	2.5
Panic Attack	10.5 (8.0-13.0)	2.5
Any psychiatric disorder	47.9	
Drug dependence	12.5 (10.2-14.8)	-

HCSUS= HIV Cost and Services Utilization Study; NHSDA=National Household Survey on Drug Abuse; *23% women; 33% Black; 15% Hispanic; ~90% aged 18-49 years; 52% ≤ high school education

Women are more cognitively vulnerable than men with HIV

- Strongest evidence available indicates a higher prevalence of cognitive impairment in women vs. men with HIV
- Largest differences are in **memory & learning** followed by processing speed & motor; inconsistent findings in executive function

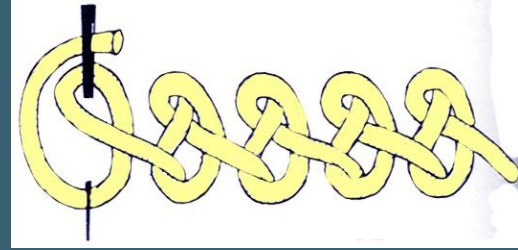
Higher 12 month prevalence of PTSD in women vs. men in the MWCCS

	People with HIV		People without HIV	
	Men (n=280)	Women (n=527)	Men (n=232)	Women (n=222)
n (%)				
Major Depression	36 (13)	56 (11)	17 (7)	24 (11)
Bipolar Disorder	3 (1)	4 (<1)	1 (<1)	2 (<1)
PTSD	50 (18)	133 (25)	35 (15)	64 (29)
Anxiety disorders	75 (27)	157 (30)	54 (23)	79 (36)
Alcohol use disorder	17 (6)	13 (2)	14 (6)	10 (5)
Substance use disorder	20 (7)	27 (5)	4 (1)	21 (10)

Women with HIV may be at an increased risk for brain health complications due to:

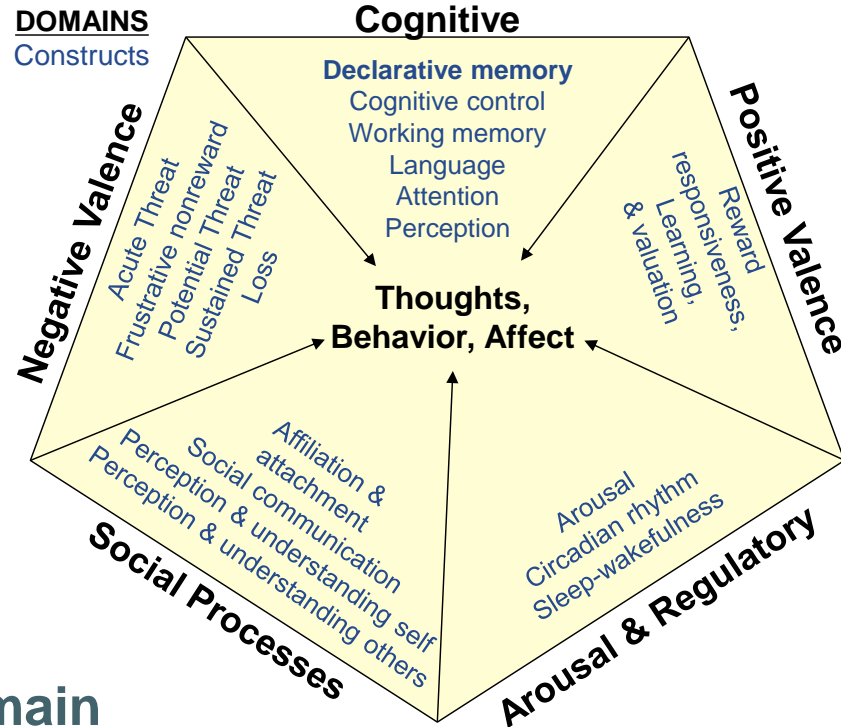
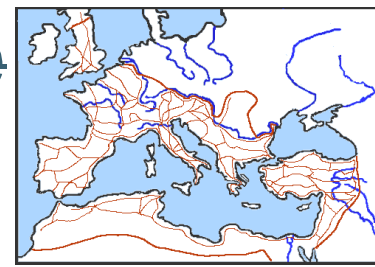
- Poverty
- Low literacy levels
- Low educational attainment
- Trauma exposure
- Substance abuse/substance use disorders
- Barriers to health care services
- Environmental exposures
- Biological factors
 - Sex steroid hormones
 - Female-specific hormonal milieus (e.g., pregnancy, menstrual cycle)

Current quagmire for IMPAACT network



What is the underlying etiology of brain health complications in women with HIV?

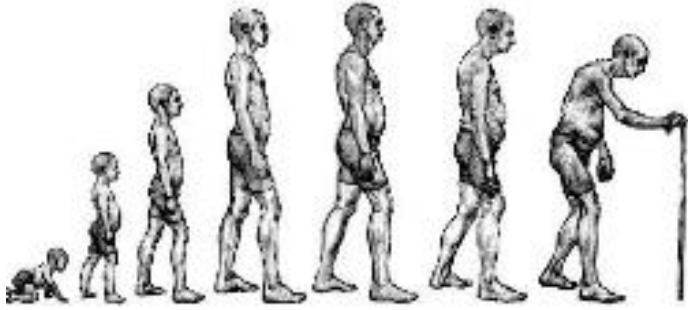
There are many roads to Rome brain health complications



**NIMH Research Domain
Criteria (RDoC)**

Modified from
Schizophrenia Bulletin
2016 Oxford University
Press

Stress Burden ['multiple hits'] Across Life



increasing burden of **ongoing**

**Congenital

childhood

adolescence

adulthood

*TOXIN EXPOSURE - MALNUTRITION - NEGLECT - ABUSE - POVERTY
- TRAUMA - STIGMA - ADVERSE LIFE EVENTS - **CHRONIC ILLNESS** (e.g.,
HIV) - ART - NON-ART MEDICATIONS*

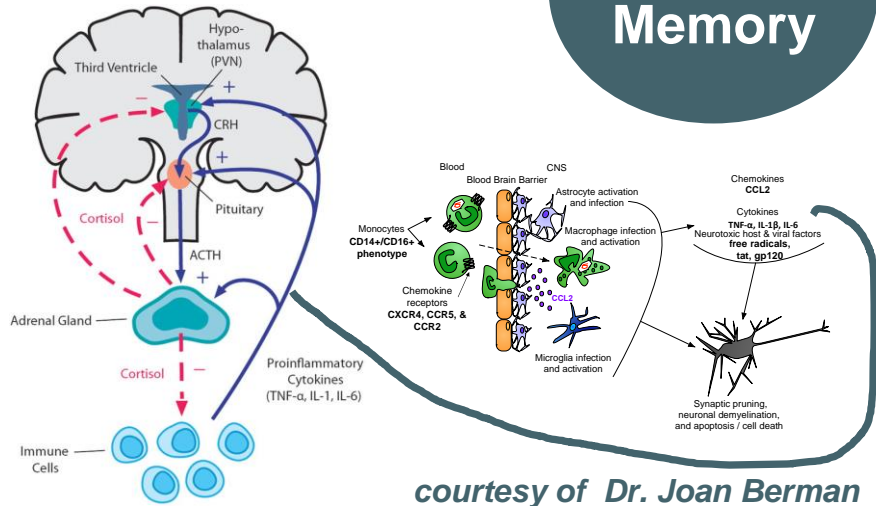
Brain health

(e.g., ANXIETY, DEPRESSION, PTSD, COGNITIVE IMPAIRMENT)

What contributes to declarative memory dysfunction in women with HIV?

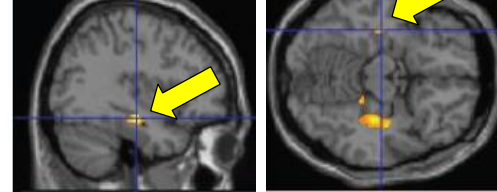
Mechanisms

Hormonal & inflammatory



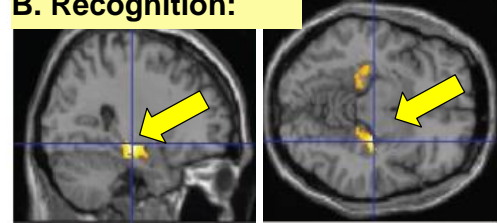
Silverman et al., *Annals of the NYAS* (2012)

A. Encoding words:



↓ HI activity
in WWH vs.
WWoH

B. Recognition:

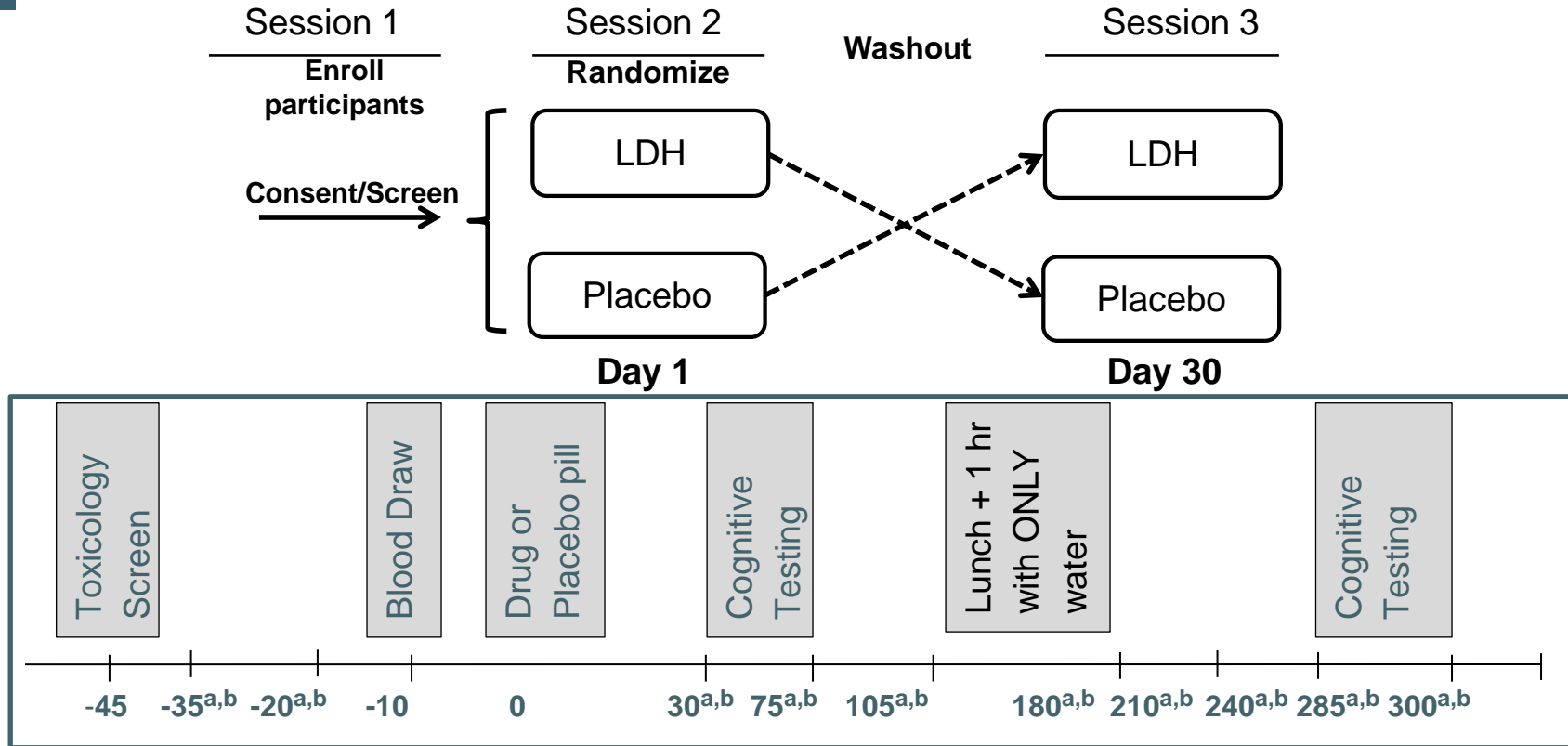


↑ HI activity
in WWH vs.
WWoH

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

WWH=women with HIV; WWoH=women without HIV

Probing the HPA axis & inflammation using low dose hydrocortisone (LDH)



^a Salivary cortisol samples measured; ^b State-Trait Anxiety Inventory-6, Visual Analog Scale Completed

Eligibility criteria

Inclusion:


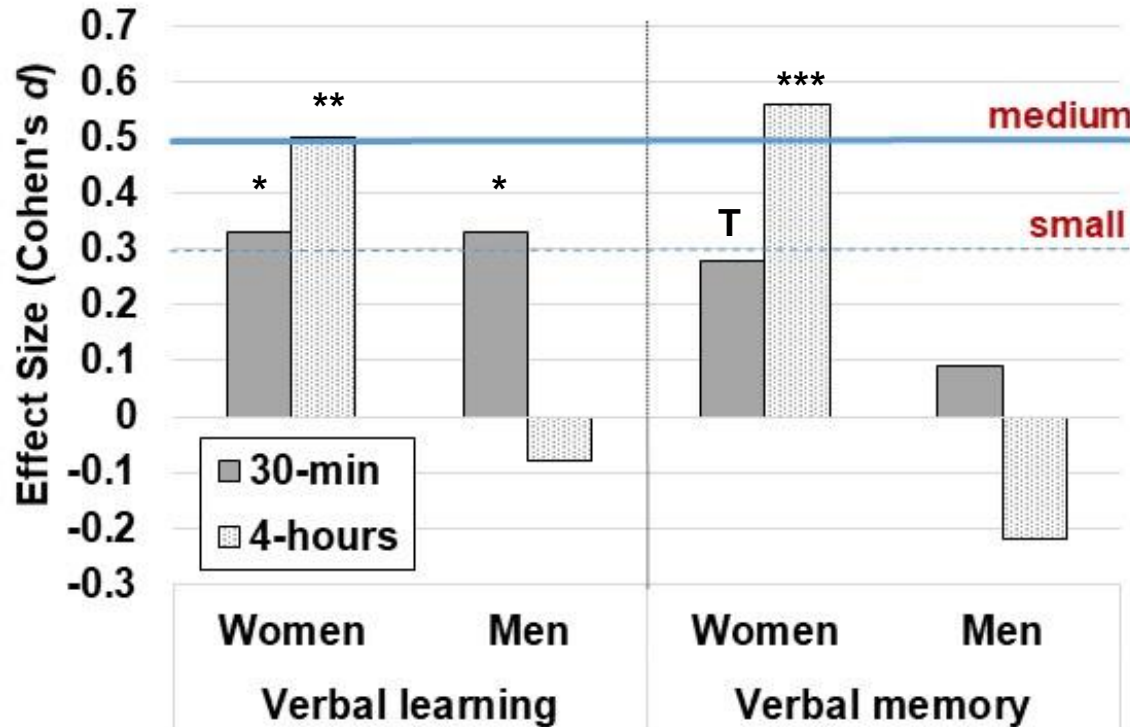
- People with HIV aged between 18 & 45
 - English as first language
 - On ART for at least 3 months
-

Exclusion:

- Current use of hormone-based contraceptives; pregnant, post-partum or lactating; regular steroid use;
- History of closed head injury resulting in loss of consciousness >1 hour
- Axis I mood or anxiety disorder in the past month
- History of psychosis, dementia or any other neurologic CNS or AIDS-defining disorder; substance use disorder in past six months
- Positive urine toxicology screen (except marijuana)
- Body mass index >40

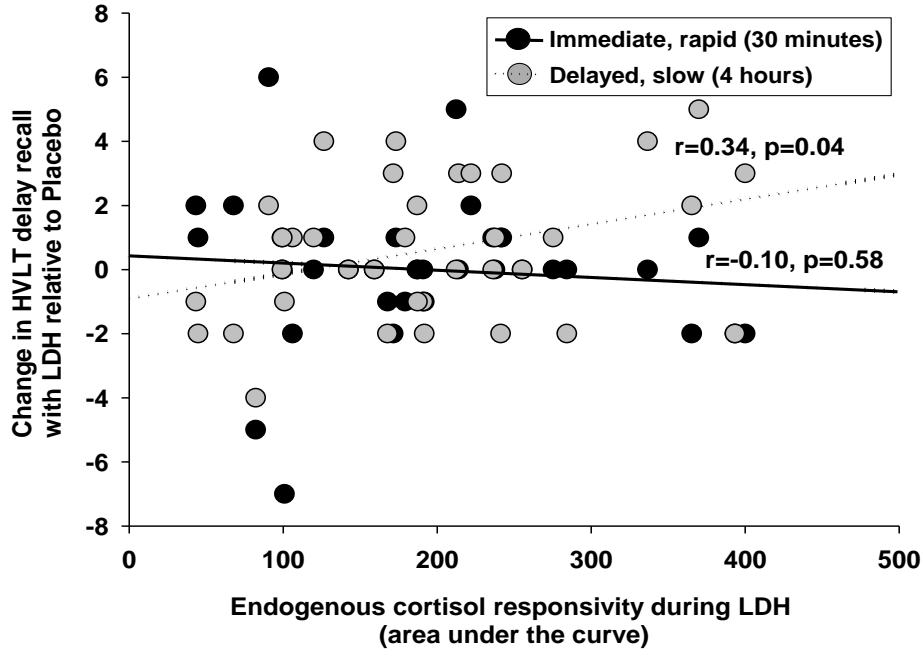
Low dose hydrocortisone (LDH) improves learning and memory in women with HIV

LDH improves performance vs. placebo

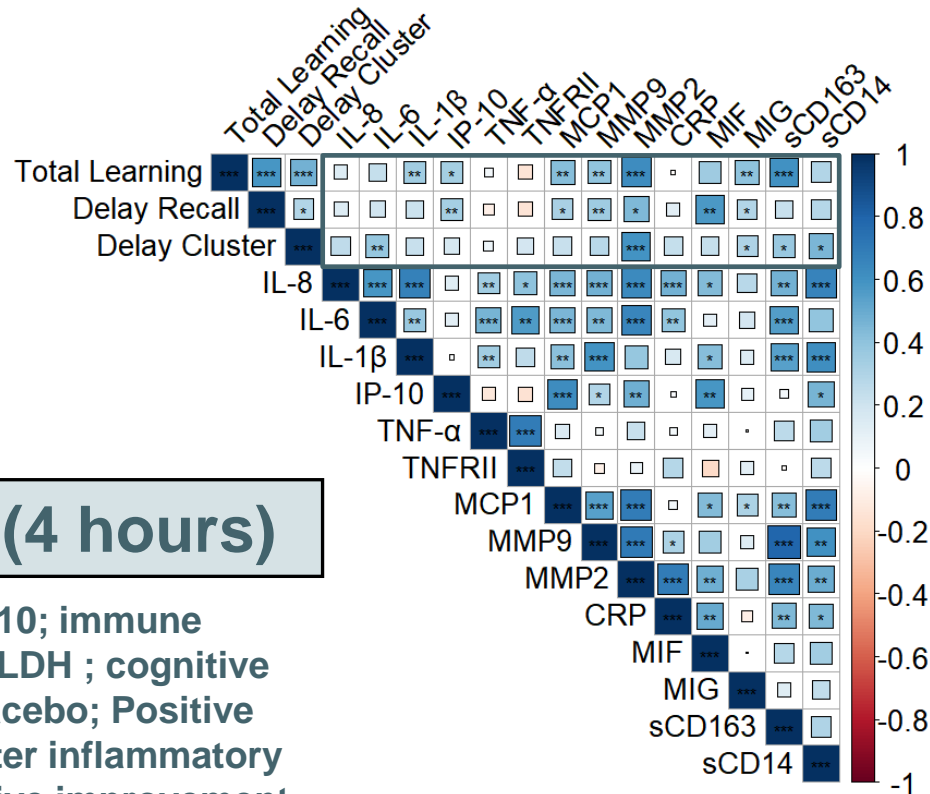
Low dose hydrocortisone (LDH) improves learning & memory in WWH via increasing cortisol responsivity

Enhanced performance with LDH vs. placebo



Greater
responsivity

Low dose hydrocortisone (LDH) improves learning & memory in WWH via suppressing inflammation



Delayed, slow (4 hours)

***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

Effects of glucocorticoids (GC) on cognition in

WWH

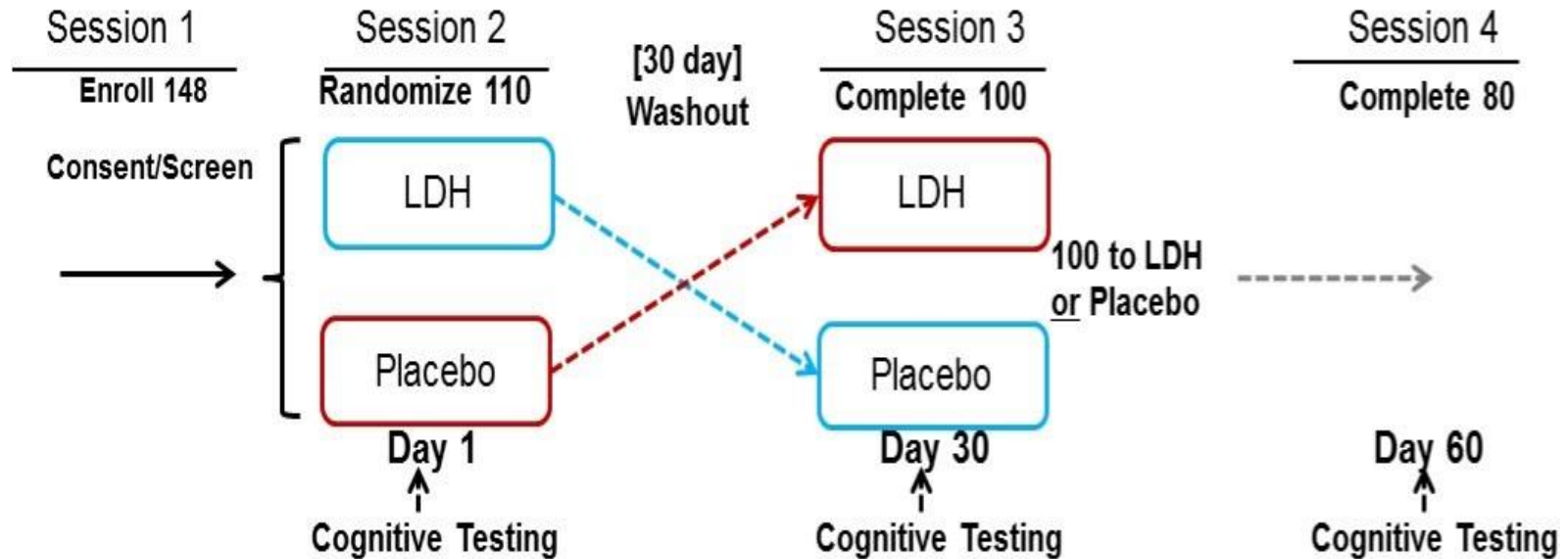
Aim 1: To examine immediate and delayed effects of a single administration of LDH on cognition in WWH.

Aim 2: To examine the effects of a 4-week course of daily LDH on cognition in WWH (Phase 0 RCT)

Aim 3: To examine potential mechanisms of LDH effects on cognition

Effects of glucocorticoids (GC) on cognition in WWH

Fig Methods to assess changes in cognition. *Double-blind placebo controlled cross-over study followed by a clinical investigation of LDH vs placebo.*



Eligibility criteria

Inclusion:

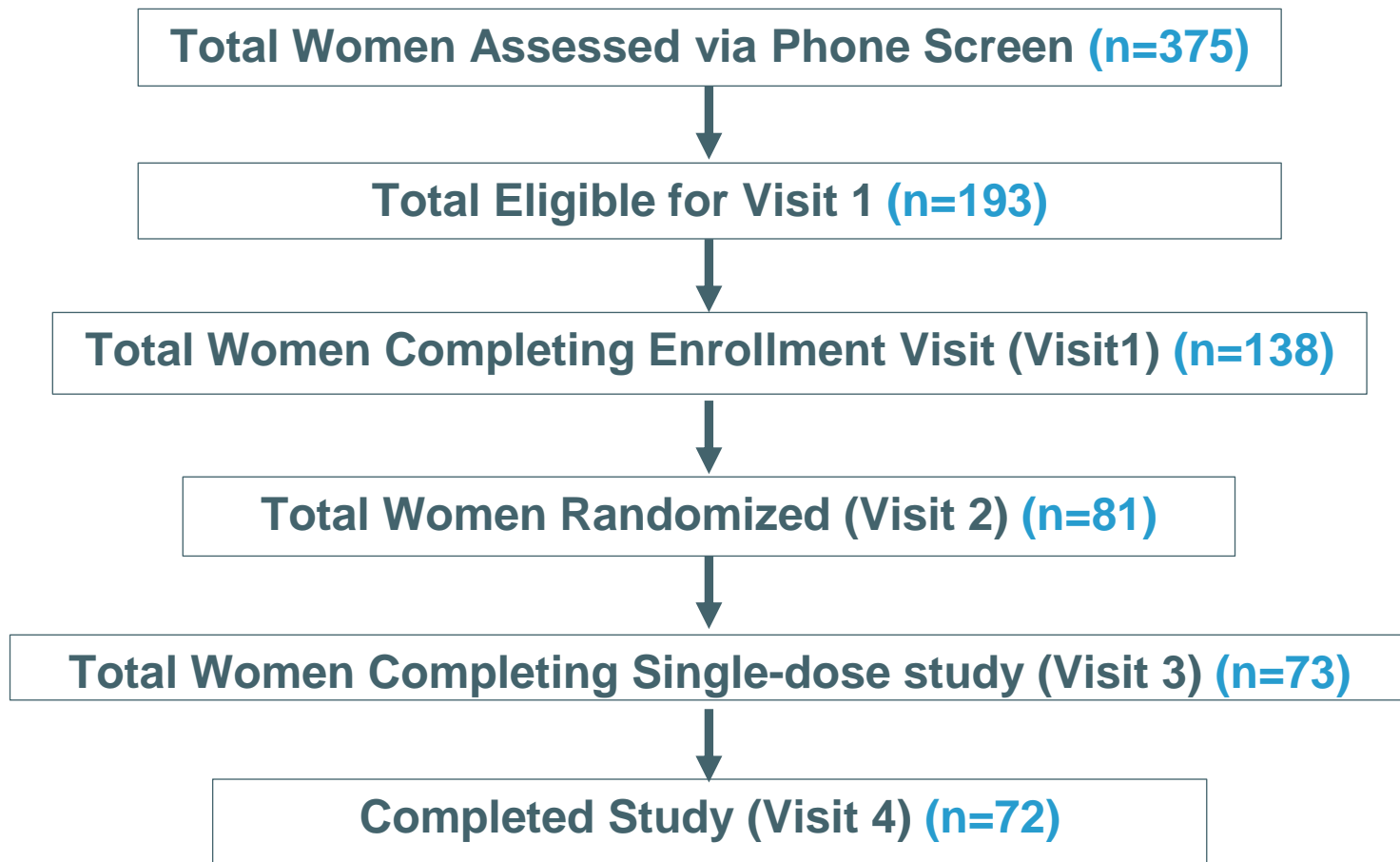
- Women with HIV aged between 18 & 65
 - Above-average self-reported levels of perceived stress (>14 on the perceived stress scale &/or current SCID-V diagnosis of mood &/or anxiety disorder
 - Meet criteria for cognitive impairment on ≥ 1 domain (via neuropsychological testing)
 - Virally suppressed & on ART (Plasma HIV RNA < 1000cp/ml)
-

Exclusion:

- Current use of hormone-based contraceptives; pregnant, post-partum or lactating; regular steroid use;
- History of closed head injury resulting in loss of consciousness >1 hour
- Current untreated hypertension or diabetes
- History of psychosis, dementia or any other neurologic CNS or AIDS-defining disorder; substance use disorder in past six months
- Positive urine toxicology screen (except marijuana) or breathalyzer

Study flow chart

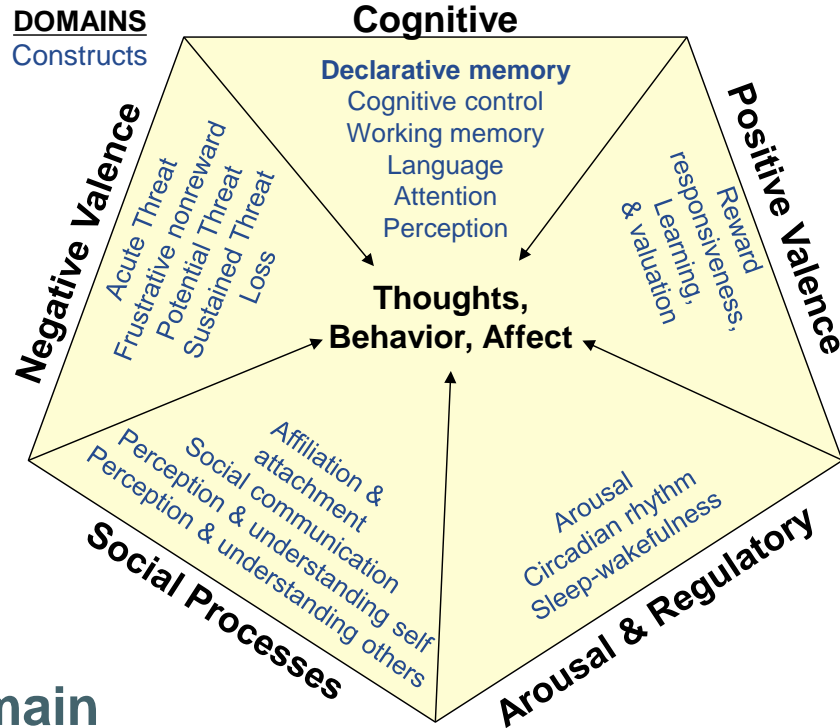
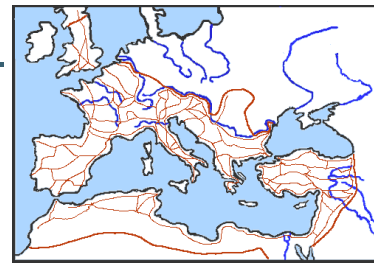
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Where do we go from here?

There are many roads to Rome

brain health complications



**NIMH Research Domain
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Modified from
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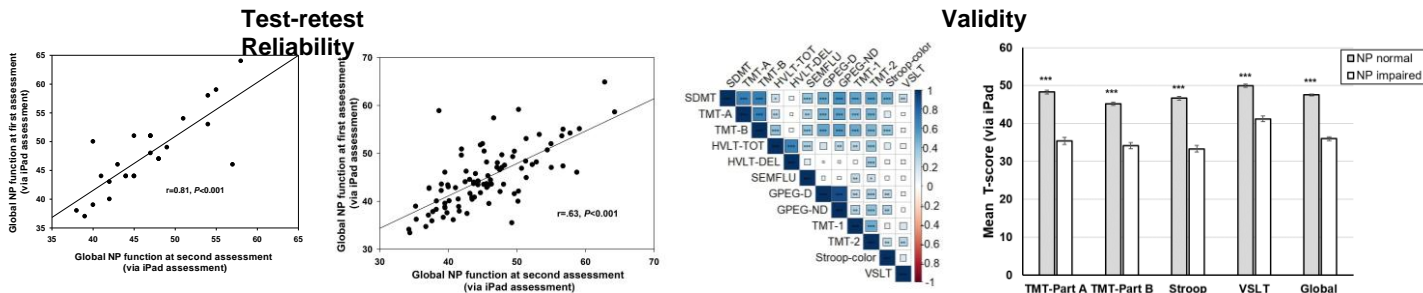
JMIR MENTAL HEALTH

Rubin et al

[Original Paper](#)

Tablet-Based Cognitive Impairment Screening for Adults With HIV Seeking Clinical Care: Observational Study

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THANKS!



[Brain Health Program | Johns Hopkins Neurology and Neurosurgery \(hopkinsmedicine.org\)](http://hopkinsmedicine.org)

Any questions?

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National Institutes
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- Kathleen Weber

Community Organization Partners

- Older Women Embracing Life (OWEL)

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