Assessment and Management of HIV Neurocognitive Disorders: Implications for Practice and Research

David E. Vance, Ph.D., MGS
Professor & Interim Associate Dean for Research,
School of Nursing &
University of Alabama at Birmingham (UAB)

Keep in Mind

- Do you purposely do things to keep your brain sharp?
- If so, what do you do to keep your brain sharp?
- Do you expect to have your same level of mental functioning 20 years from now?
- Do you ask your patients about what they do to help their brain to age? (and if you do, do you know what to tell them?)
  - 4 Focus Groups → 30 Older Adults with HIV
    - Gross understanding that keeping active is important for brain health.
    - Passive acceptance of decreased brain function (*Nothing we can do!*).

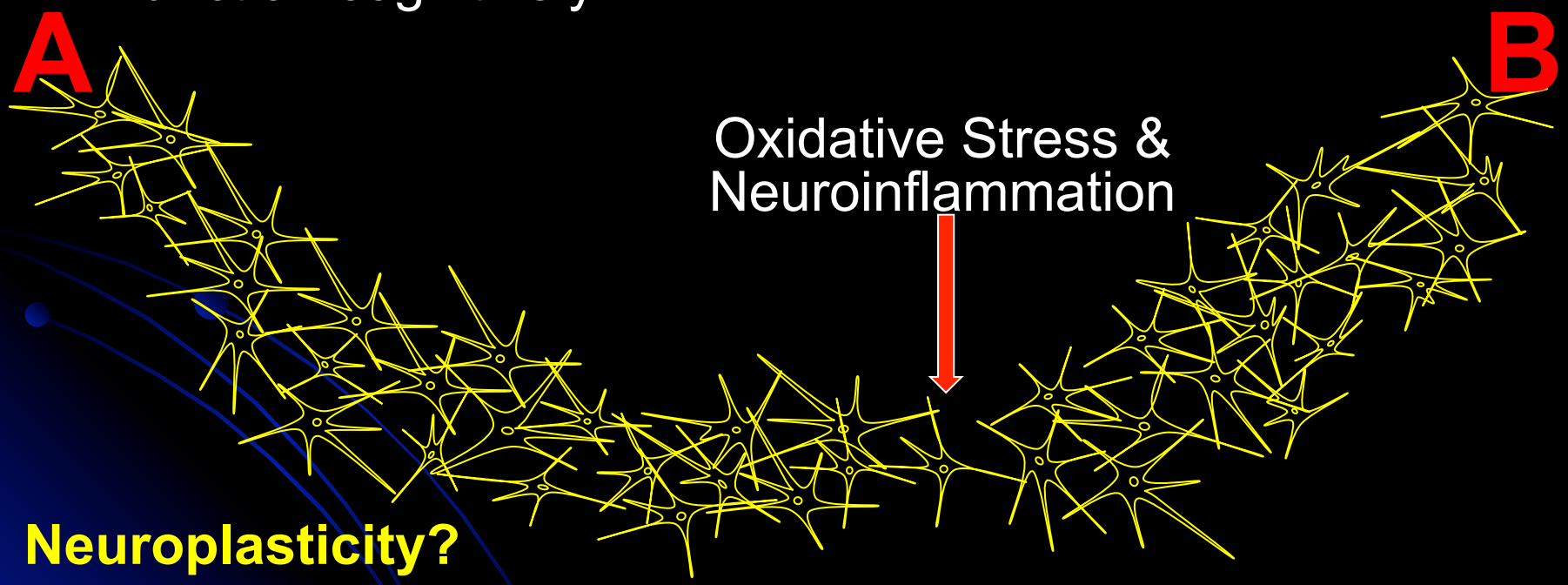
Learning Objectives

- ✓ Review possible causes of neurocognitive impairment in adults with HIV, especially as they age.
- ✓ Provide methods of assessing cognitive deficits in adults with HIV.
- ✓ Present evidence-based recommendations for treating and addressing neurocognitive problems in patients with HIV.

COGNITIVE RESERVE

Cognitive/Neurological Resources

- Cognitive Reserve Hypothesis – The greater the strength and sophistication between neurons, the better able one can weather neurological insults and still function cognitively.



Neuroplasticity?
Probably plays a larger degree.

Positive and Negative Neuroplasticity

- **Enriched Environmental Paradigm**

Enriched Environment

Standard Environment

Placed 3 to a cage, with no toys

Impoverished Environment

Placed in isolation, with no toys

Positive Neuroplasticity

- The brain builds more sophisticated and more connections between neurons.
- Better Cognitive Reserve

Studies in the aging and HIV literature show that increased cognitive activity, which reflects an enriched environment, promotes optimal cognitive functioning.

Negative Neuroplasticity

- The brain atrophies quicker with less sophisticated and less connections between neurons.
- Poorer Cognitive Reserve

Neuroplasticity

Positive Neuroplasticity

More Environmental Complexity; More Novelty

Greater Cognitive Reserve; Better Cognitive Functioning

Novelty ↕ **Cognitive Reserve**

Less Environmental Complexity; Less Novelty

Poorer Cognitive Reserve; Worse Cognitive Functioning

Negative Neuroplasticity

Enriched Environment

Standard Environment

Impoverished Environment

Enriched Environment Paradigm
(Diamond, 1993)

Learned to juggle within 3 months (MRI @ Time 2)

Stopped juggling after 3 months of learning (MRI @ Times 1, 2. & 3)

Older Jugglers Study
(Boyke et al., 2008)

Taxi Drivers

- Studied 2-4 years
- Learned different points of interest
- Learned 25,000 streets
- Variable routes

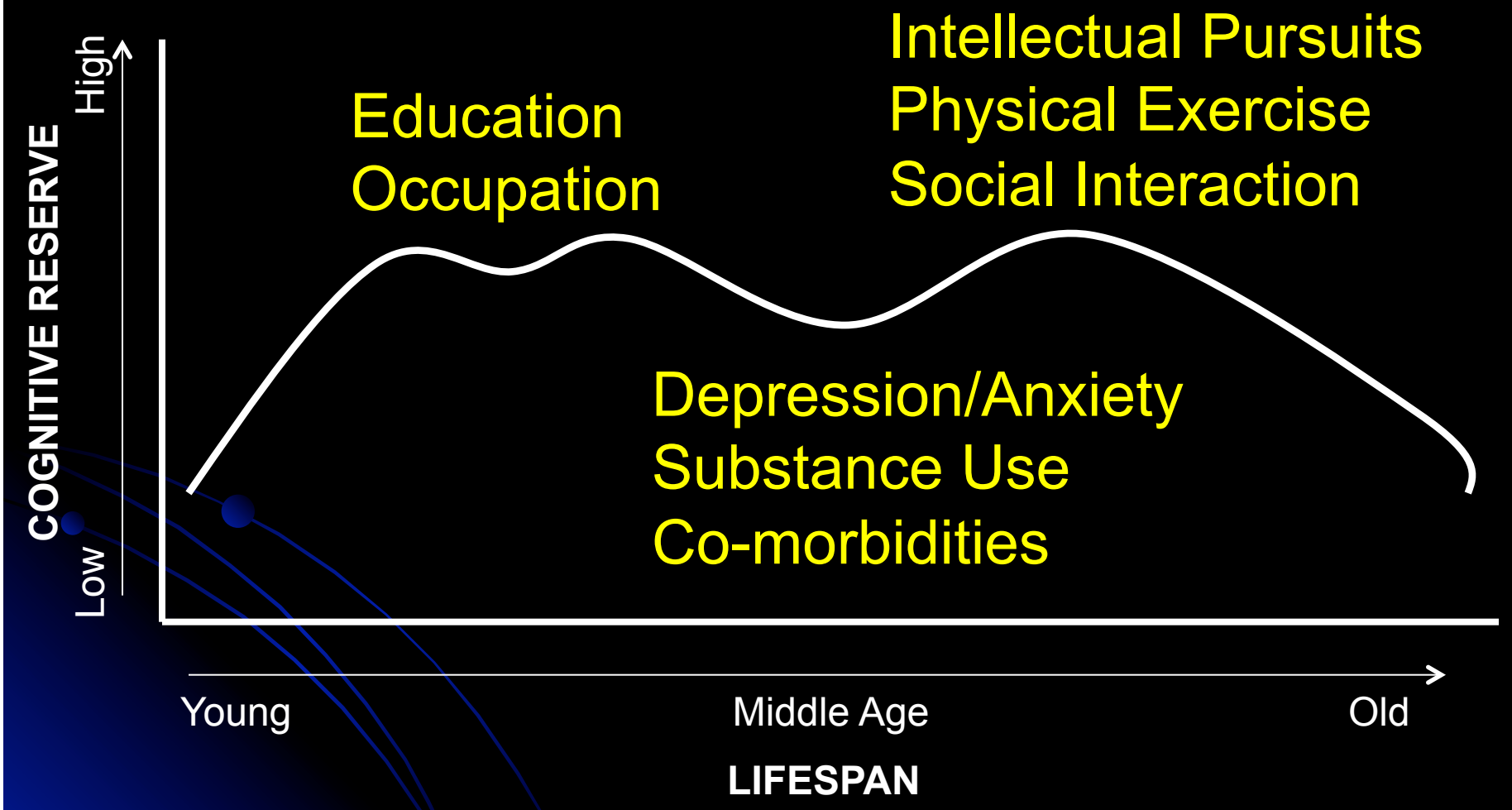
Bus Drivers

- Shorter training period
- Set route

London Taxi Driver Study
(Maguire et al., 2006)

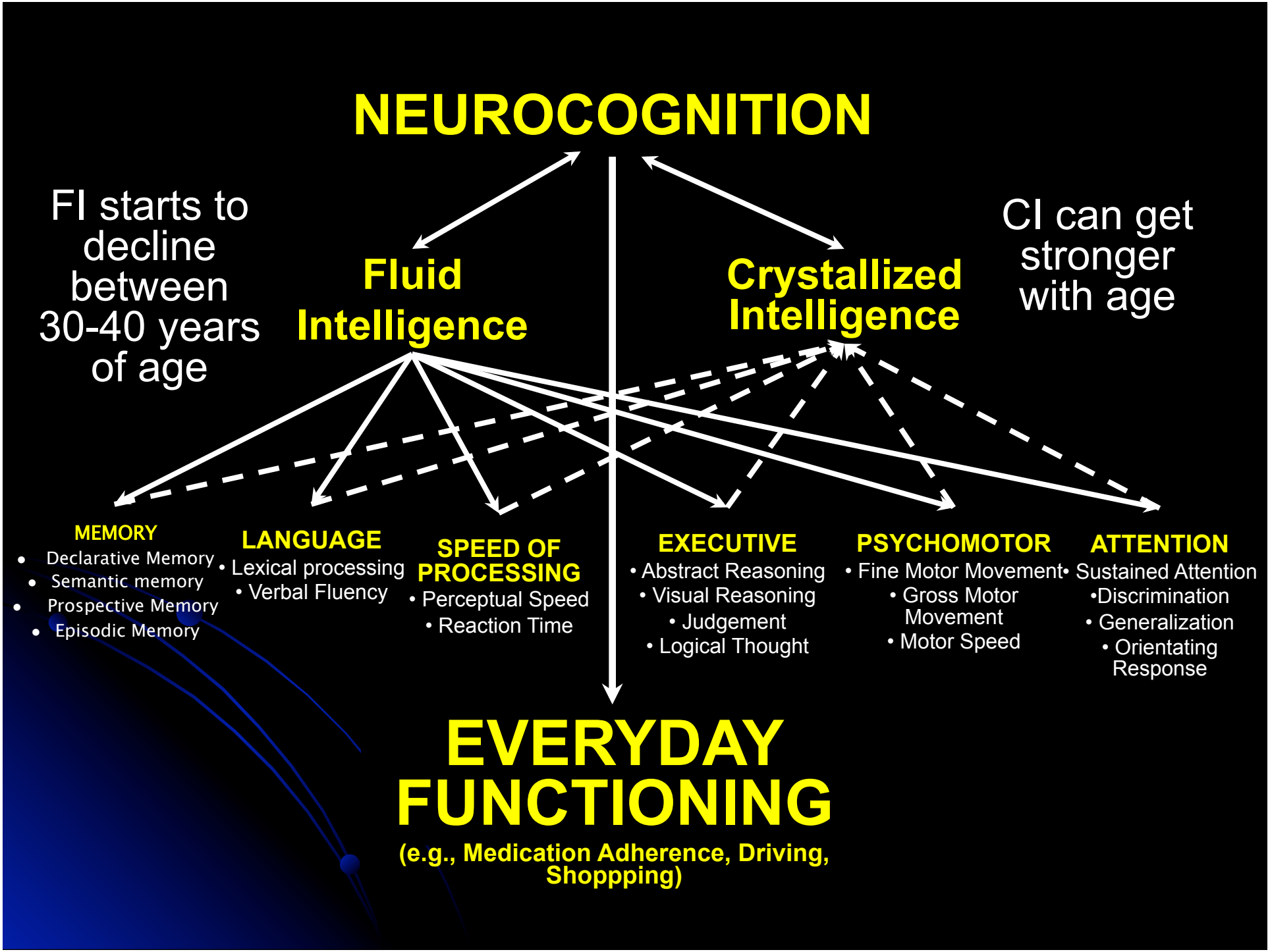
Vance, D. E., Kaur, J., Fazeli, P. L., Talley, M. H., Yuen, H. K., Kitchin, B., & Lin, F. (2012). Neuroplasticity and successful cognitive aging: A brief overview for nursing. *Journal of Neuroscience Nursing*, *44*(4), 218-227. DOI: 10.1097/JNN.0b013e3182527571

Cognitive Reserve over the Lifespan



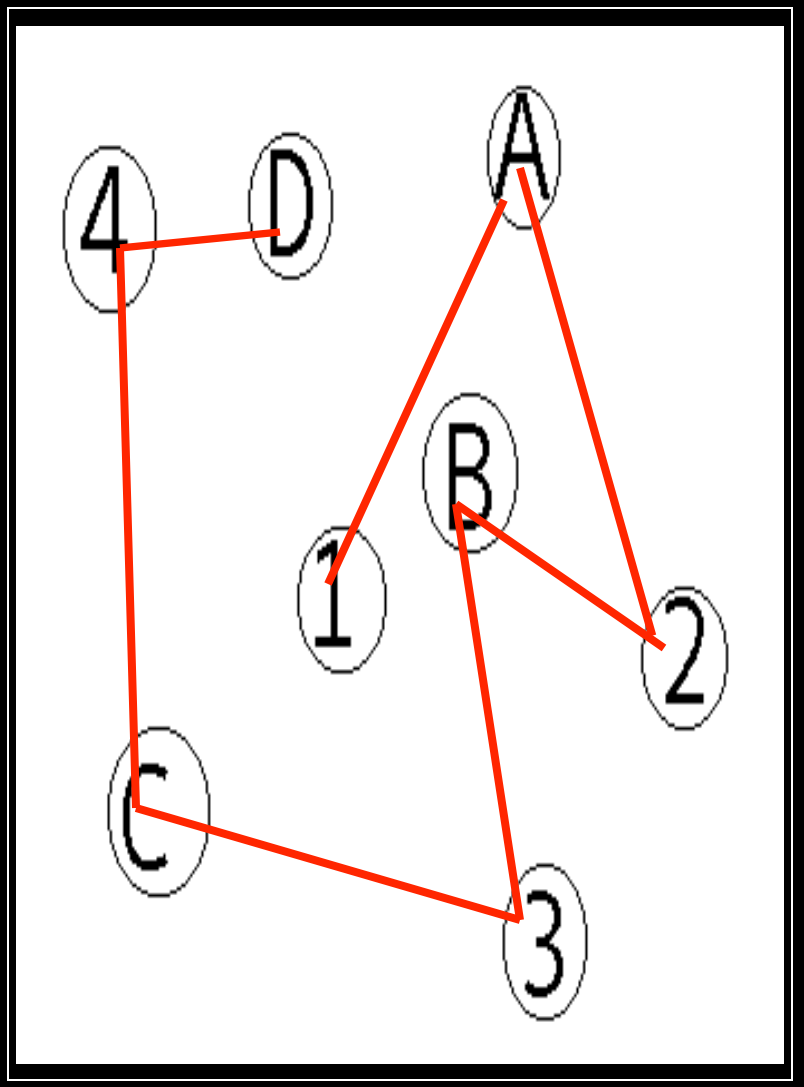
Vance, D. E., Muñoz-Moreno, J., Lee, L., Morrison, S., Overton, T., Willig, A., & Fazeli, P. L. (under review). Cognitive reserve over the lifespan: Neurocognitive implications for aging with HIV. Journal of the Association of Nurses in AIDS Care.

HIV & COGNITION


NEUROCOGNITION
FI starts to decline between 30-40 years of age
Fluid Intelligence
Crystallized Intelligence
CI can get stronger with age
MEMORY
• Declarative Memory
• Semantic memory
• Prospective Memory
• Episodic Memory
LANGUAGE
• Lexical processing
• Verbal Fluency
SPEED OF PROCESSING
• Perceptual Speed
• Reaction Time
EXECUTIVE
• Abstract Reasoning
• Visual Reasoning
• Judgement
• Logical Thought
PSYCHOMOTOR
• Fine Motor Movement
• Gross Motor Movement
• Motor Speed
ATTENTION
• Sustained Attention
• Discrimination
• Generalization
• Orientating Response
EVERYDAY FUNCTIONING
(e.g., Medication Adherence, Driving, Shoppping)

Trails B – Executive Functioning

"On this page are both numbers and letters. Begin at number 1 **(point to 1)** and draw a line from 1 to A **(point to A)** A to 2 **(point to 2)** 2 to B **(point to B)** and so on until you reach the circle marked 'End'."



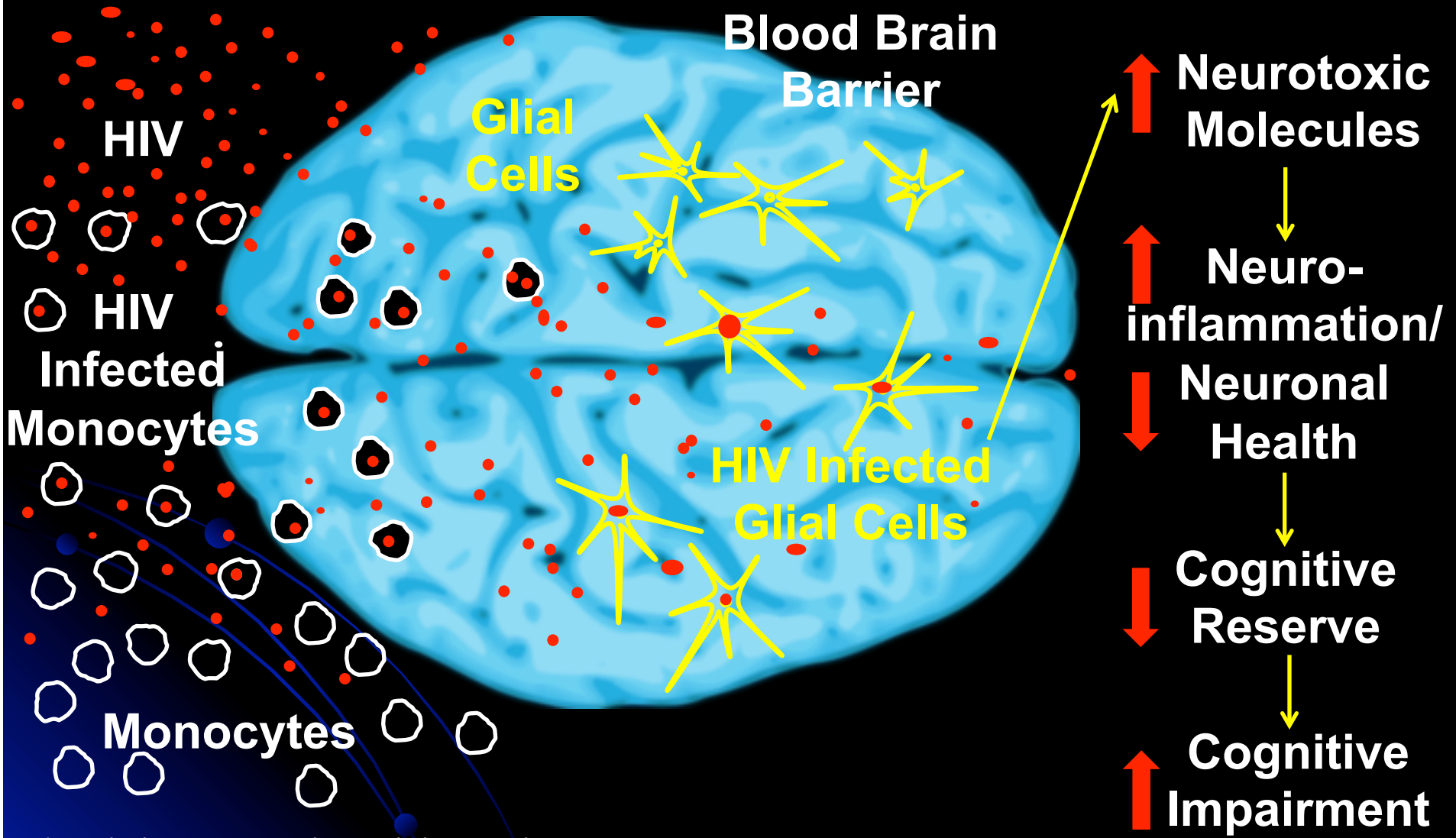
Clinical Observation:

Social graces may still be intact while someone performs poorly on these tests.

How soon are cognitive changes detected with HIV? 1, 3, 5, 8 years?

- Cognitive changes occur quickly, slowly, or not at all.
- Changes in brain metabolism and cognition have been detected in many adults **just 1 year after diagnosis** (Basso & Bornstein, 2000; Bornstein et al., 1993; Lentz et al., 2011).
  - Yet, a high degree of variability.
- Those with **better premorbid intelligence** experienced **fewer cognitive declines** (Basso et al., 2000; Bornstein et al., 1993).
- In an **8-year longitudinal study**, compared to those without HIV, those with HIV experience significant declines in speed of processing and psychomotor function, especially if they **progressed to AIDS**. (Baldewizc et al., 2004).

Does HIV infect neurons in the brain? NO



* It is both monocytes and particularly macrophages.

Vance, D. E., Humphrey, S. C., & Batey, D. S. (in press). HIV-related cognitive dysfunction: Implications for aging and social work. *Social Work in Mental Health.*

FRASCATI CRITERIA

- **HIV-Associated Neurocognitive Disorder (HAND) Criteria**

- **Asymptomatic Neurocognitive Impairment (ANI)**
  - > 1 SD normative mean on at least 2 cognitive domains (attributable to HIV)
- **Mild Neurocognitive Disorder (MND)**
  - > 1 SD normative mean on at least 2 cognitive domains (attributable to HIV)
  - Mild functional decline (e.g., self/proxy-report of decline in 2 ≥ IADLs, vocational impairment, poor performance in laboratory based IADLs)
- **HIV-Associated Dementia (HAD)**
  - > 2 SD normative mean on at least 2 cognitive domains (attributable to HIV)
  - Mild functional decline (e.g., self/proxy-report of decline in 2 ≥ IADLs, vocational impairment, poor performance in laboratory based IADLs)

How many adults with HIV have HAND? 14% 30% 50% 70%?

~20% Bi-directional Fluctuation over Time

(Antinori et al., 2007. *Neurology, 69,* 1789-1799.)

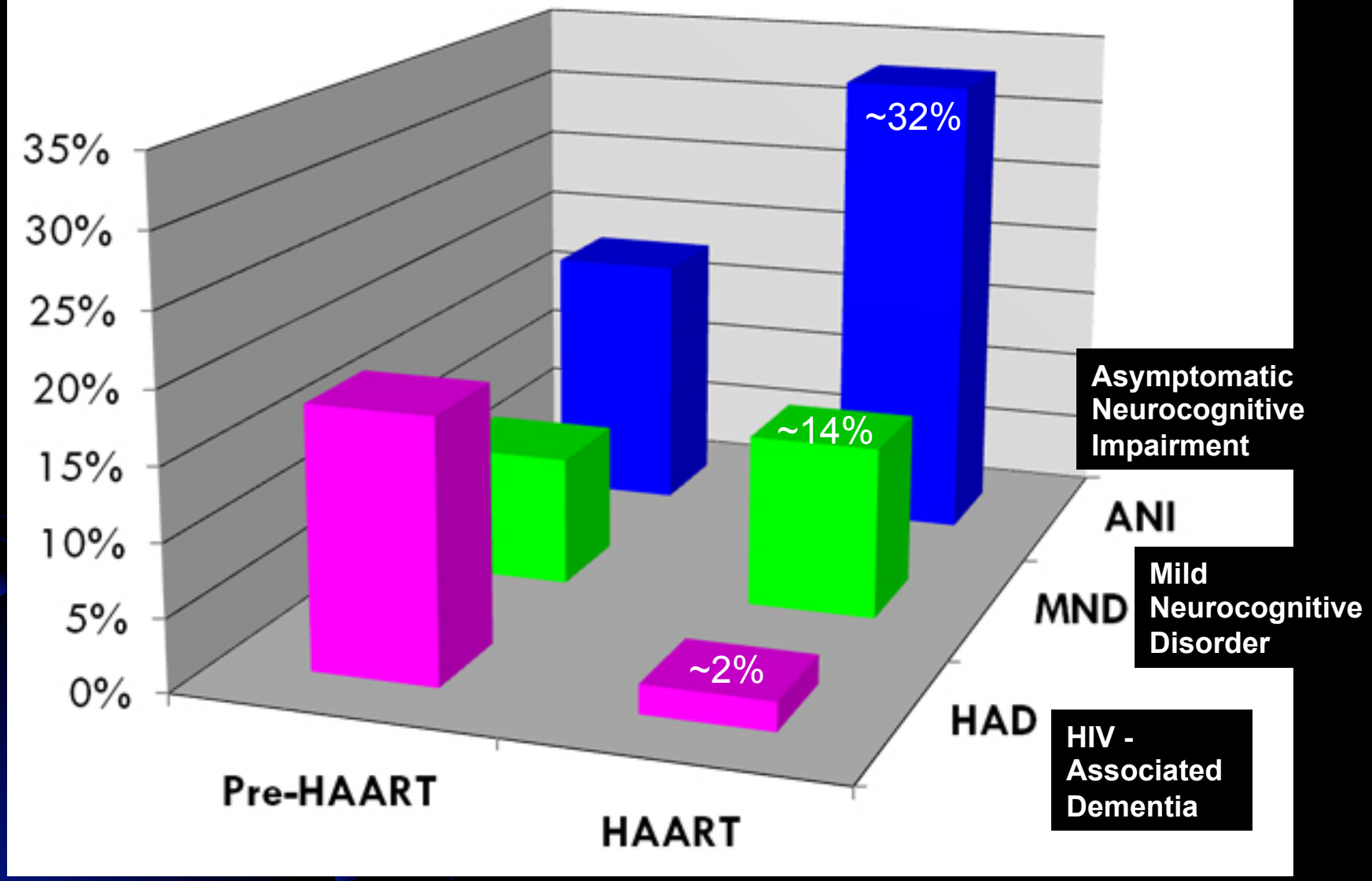


Figure 1. Note. Croteau, D. Pharmacologic interventions for HIV-associated neurocognitive disorders. *Psychology and AIDS Exchange Newsletter.* Retrieved from http://www.apa.org/pi/aids/resources/exchange/2013/01/pharmacologic-interventions.aspx

Nick.ms

- Age: 56
- AIDS Diagnosis: 2007
  - CD4 Count – 6 cells/mm^3
  - Viral Load – 800,000 copies/mL
- HAD Diagnosis: 2009
- 2010 Neuropsychological Assessment – Mixed Results
- BSW 2011 – Jackson State University (summa cum laude)
- MSW 2012 – December 2012
- 26th Annual Social Work and HIV/AIDS Conference in 2013 – "Help! I've Lost My Mind! There's an App for That!"

Nick.ms

- **2010 Neuropsychological Assessment: Mixed Results**

- "Mr. Nicholas' self-report during the clinical interview as well as his performance on the neuropsychological and achievement tests revealed **cognitive dysfunction consistent with dementia of the subcortical type** associated with HIV infection, including impairments in memory, motor speed and control, word finding, and generalized slowing of information processing speed.

- **His language functions were relatively preserved**, also consistent with dementia due to HIV infection."

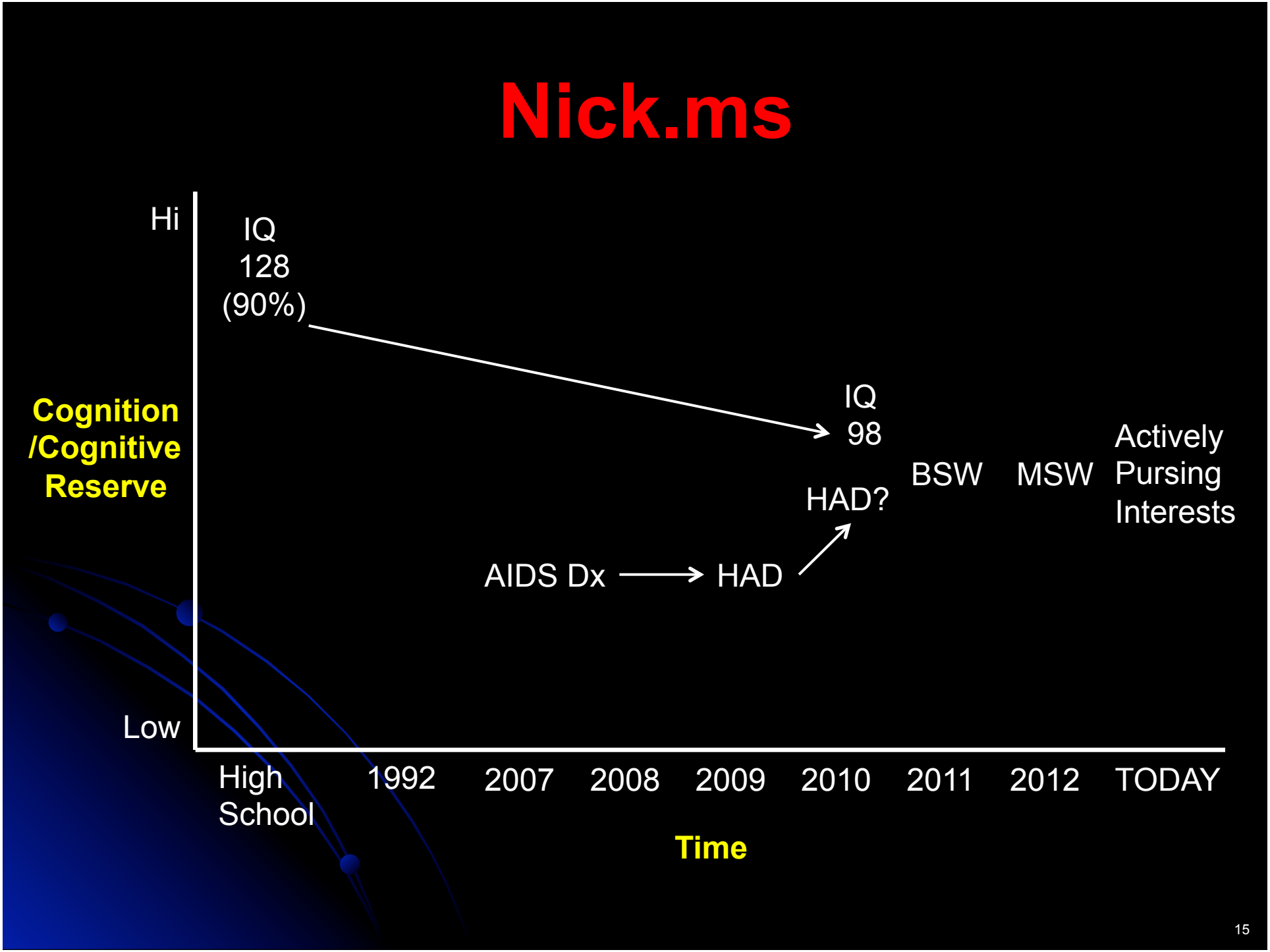
Nick.ms

- **TODAY**

- "I would often have trouble finding the word (dysnomia) I wanted to use. This was very unusual for me because I am extremely, almost frighteningly, articulate. Words would just flow out of my mouth. Not any more."

- "I used to spend hours devouring books. Now I had a hard time finishing a page. I've always been a little absent-minded… But it had become ridiculous. I don't know where it came from, except that it popped into my head one day: 'If it is not in my hands, it's lost!' That phrase is now almost a mantra! It is not an exaggeration to say I spend *hours* daily looking for items I've misplaced."

Nick.ms


Hi
IQ
128
(90%)
IQ
98
Cognition
/Cognitive
Reserve
BSW
MSW
Actively
Pursing
Interests
HAD?
AIDS Dx
HAD
Low
High
School
1992
2007
2008
2009
2010
2011
2012
TODAY
Time

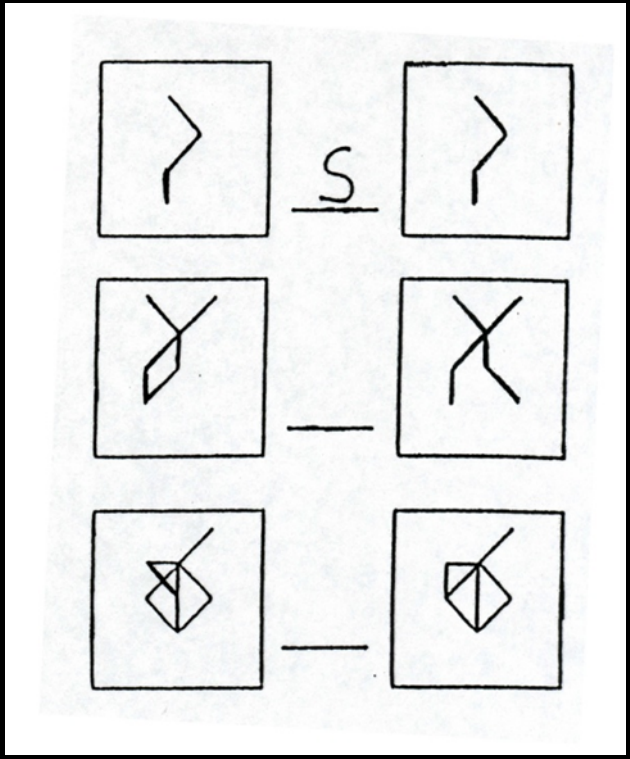


TABLE 2

Adjusted Means of Neurocognitive and Everyday Performance between Groups (N = 172)

	HIV-POSITIVE		HIV-NEGATIVE		
	YOUNGER (*n* = 55)	OLDER (n = 33)	YOUNGER (*n* = 43)	OLDER (n = 41)	FINDINGS
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	
PSYCHOMOTOR SPEED					
Finger Tapping Test (number of taps)	103.23 (14.92)	96.31 (14.73)	104.35 (14.74)	92.34 (14.50)	A‡
SPEED OF PROCESSING					
Useful Field of View (milliseconds)	693.09 (357.39)	861.12 (354.15)	530.01 (354.25)	736.00 (348.45)	A‡, H†
Complex Reaction Time (seconds)	3.76 (1.07)	4.20 (1.06)	3.26 (1.06)	3.55 (1.04)	A†, H‡
Letter Comparison (number correct)	47.34 (10.95)	41.99 (10.86)	51.17 (10.83)	44.72 (10.65)	A‡
Pattern Comparison (number correct)	33.96 (7.21)	28.77 (7.12)	36.18 (7.13)	32.13 (7.01)	A‡, H†
MEMORY FUNCTIONING					
Hopkins Verbal Learning (number correct)	24.97 (6.00)	22.32 (5.92)	24.67 (5.79)	22.64 (5.83)	A†
EXECUTIVE FUNCTIONING					
Wisconsin Card Sorting (number correct)	62.65 (18.76)	57.92 (18.50)	63.39 (18.49)	64.47 (18.25)	ns
EVERYDAY FUNCTIONING					
Timed Instrumental Activities of Daily Living (z-score composite)	-0.31 (3.05)	2.12 (2.99)	-0.57 (3.00)	-0.66 (2.96)	A†, H‡, HxA‡
Observed Tasks of Daily Living (total score)	68.43 (7.37)	66.64 (7.29)	70.13 (7.29)	69.24 (7.17)	ns

Notes: A = Age main effect detected; H = HIV main effect detected; HxA = HIV x Age interaction detected; M = mean; ns= not significant; SD = standard deviation. † = sig. at < .05; ‡ = sig. at < .01.

Vance, D. E., Fazeli, P. L., & Gakumo, C. A. (2013). The impact of neuropsychological performance on everyday functioning between older and younger adults with and without HIV. *Journal of the Association of Nurses in AIDS Care, 24*(2), 112-125.

Cluster Analysis

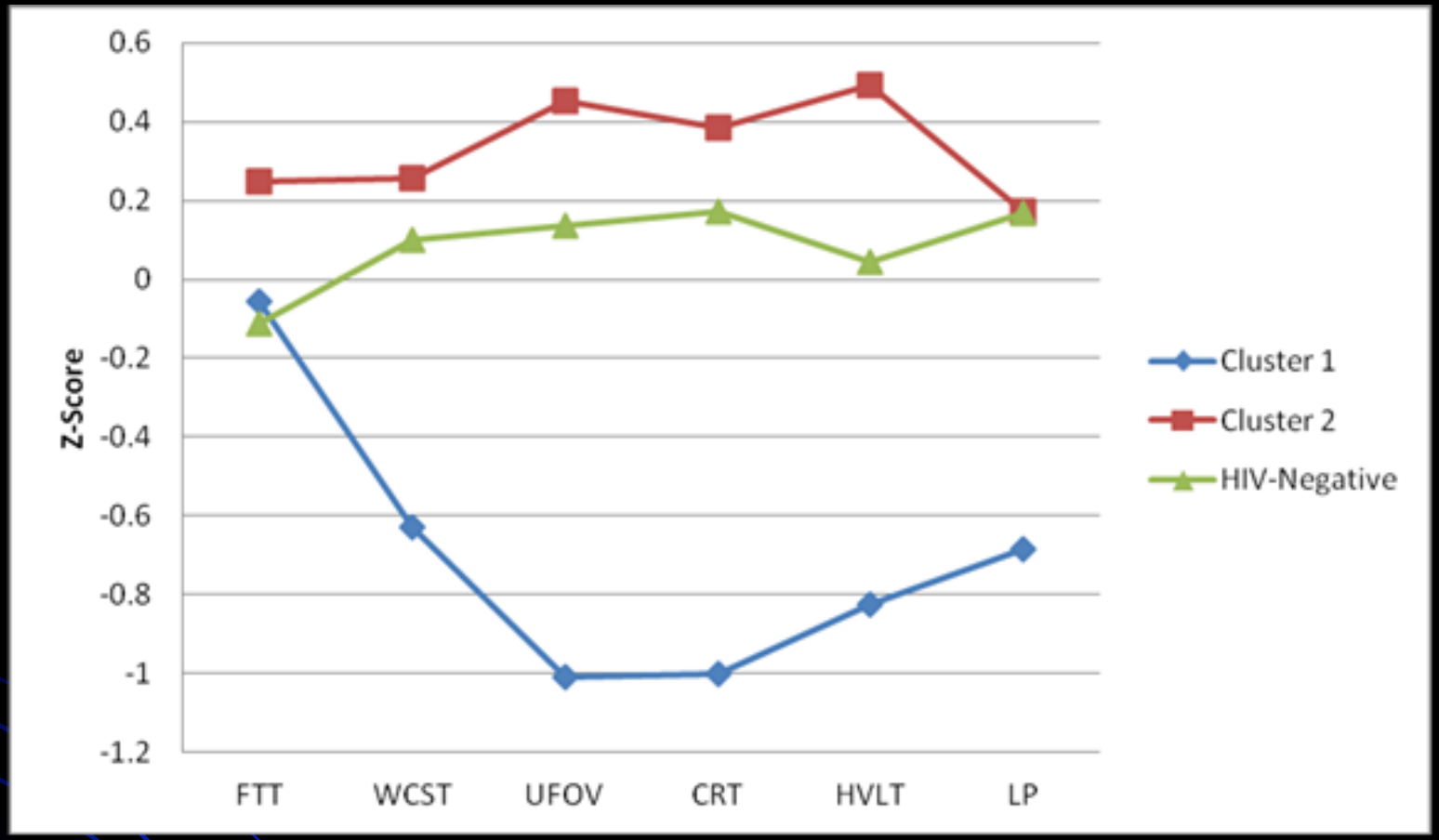


Figure 1. *Z*-scores for Cognitive Test Performance for Clusters 1 and 2, and the HIV-Negative Group. *Note.* FTT = Finger Tapping Test; WCST = Wisconsin Card Sorting Test; UFOV® = Useful Field of View; CRT = Complex Reaction Time; HVLT = Hopkins Verbal Learning Test; LP = Letter and Patter Comparison. For the purpose of clarity, higher *z*-scores reflect higher performance for all variables.

Fazeli, P. L., Crowe, M., Ross, L. A., Wadley, V., Ball, K. K., & Vance, D. E. (2014). Cognitive functioning in adults aging with HIV: A cross-sectional analysis of cognitive subtypes and influential factors. *Journal of Clinical Research in HIV/AIDS and Prevention, 1*(4), 1-12. DOI: 10.14302/issn.2324-7339.jcrhap-13-191

Table 5
Demographic and Mental and Physical Health Differences of the HIV+ Clusters and the HIV-Negative Reference Group (Total $N = 162$)

	Cluster						
	Cluster 1 ($n = 32$)		Cluster 2 ($n = 46$)		HIV- Group ($n = 84$)		
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*p*-value
Age	51.27	10.84	43.36	8.83	47.93	13.06	< .05 [a]
No. Over Age 50 (%)	19 (59%)		12 (26%)		41 (49%)		< .01 [a, c]
No. Men (%)	22 (69%)		37 (80%)		33 (39%)		< .05 [b, c]
No. Heterosexuals (%)	20 (63%)		19 (41%)		78 (93%)		< .05 [b, c]
No. Caucasians* (%)	8 (25%)		21 (46%)		29 (36%)		*ns*
No. Working (%)	2 (6%)		10 (22%)		35 (42%)		< .001 [b, c,†]
Income	1.56	0.84	1.87	1.61	1.98	1.53	*ns*
Education (years)	12.66	2.51	12.85	2.49	12.79	1.68	*ns*
No. Med. Conditions	1.94	1.24	1.34	1.02	1.06	0.99	< .01 [a, b]
No. w/ Hepatitis C (%)	14 (44%)		12 (26%)		6 (7%)		< .001 [b, c,†]
No. w/ Mood Prob. (%)	18 (56%)		26 (57%)		33 (39%)		*ns*
No. w/ Stroke (%)	6 (19%)		1 (2%)		5 (6%)		< .05 [a, b]
No. w/ Hypertension (%)	20 (63%)		18 (39%)		32 (38%)		< .05 [a, b]
No. w/ Diabetes (%)	4 (13%)		5 (11%)		10 (12%)		*ns*
No. Medications	5.25	3.85	4.54	3.04	2.18	2.74	< .001 [b, c]
POMS Total	35.59	32.94	35.39	45.05	28.26	37.89	*ns*
POMS-Positive	16.94	6.43	18.28	6.87	19.27	6.52	*ns*
POMS-Negative	52.53	30.55	53.67	40.53	47.54	34.87	*ns*
Stressful Life Events	263.56	151.71	271.59	132.10	238.51	164.16	*ns*
ASI-Alcohol Use	0.07	0.15	0.35	0.75	0.24	0.45	*ns*
ASI-Drug Use	0.03	0.06	0.03	0.08	0.02	0.04	*ns*

Fazeli, P. L., Crowe, M., Ross, L. A., Wadley, V., Ball, K. K., & Vance, D. E. (2014). Cognitive functioning in adults aging with HIV: A cross-sectional analysis of cognitive subtypes and influential factors. *Journal of Clinical Research in HIV/AIDS and Prevention, 1*(4), 1-12. DOI: 10.14302/issn.2324-7339.jcrhap-13-191

Predictors of Neurocognition in Adults with HIV

Other predictors of neurocognitive functioning are reported in adults with HIV.

- Stress, Depression, Anxiety, Post-traumatic Stress
- Age
- Income
- Educational Level/Attainment
- Reading/Reading Quality
- Insulin Resistance
- Hepatitis C/Liver Fibrosis
- Cognitive Activity & Employment
- Treatment Status (viral load, CD4 count)
- Substance Use
- Head Injury
- APOE-4

Everyday Functions Compromised by Poor Cognition

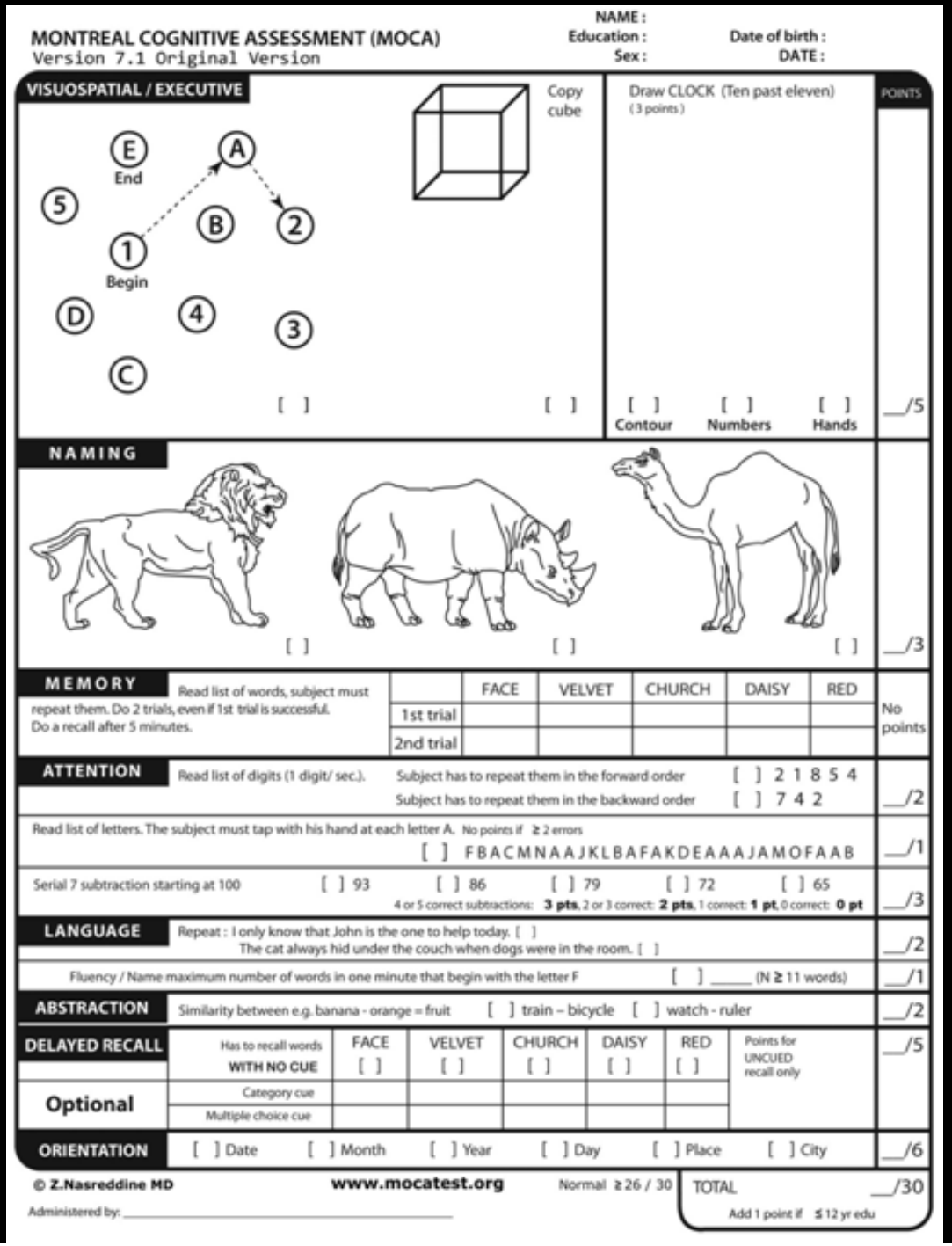
(example in HIV)

- **Instrumental Activities of Daily Living** (Heaton et al., 2004).
- **Financial and medical management** (Heaton et al., 2004).
- **Medication adherence** (Woods et al., 2009).
- **Employment** (Woods, Weber et al., 2011).
- **Prone to risky decision-making** (Hardy, Hinkin et al., 2006) & **cognitive impulsivity** (Martin et al., 2004).
- **Lower health-related quality of life** (Doyle et al., 2012).
- **Higher risk of mortality** (Ellis et al., 1997; Wilkie et al., 1998).

COGNITIVE ASSESSMENT

Global Cognitive Impairment

A score of 26 or below is indicative of cognitive problems.



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — Copy cube — Draw CLOCK (Ten past eleven) (3 points) — POINTS

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ]

[ ] Contour [ ] Numbers [ ] Hands — /5

NAMING — [ ] [ ] [ ] — /3

MEMORY — Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 — /2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B — /1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** — /3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] — /2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) — /1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler — /2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

— /5

ORIENTATION — [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City — /6

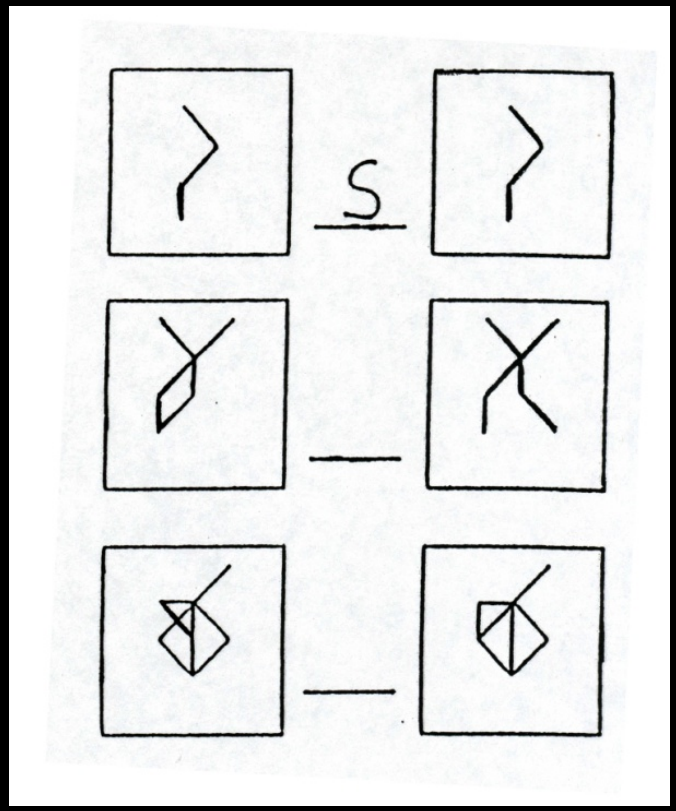
© Z.Nasreddine MD — www.mocatest.org — Normal ≥ 26 / 30

TOTAL — /30
Add 1 point if ≤ 12 yr edu

Administered by: _____

Neuropsychological Battery (~ 2 hours)

- **Neuropsychological Battery (Different Domains)**
  - **Speed of Processing (Fluid)**
    - Useful Field of View Test (UFOV®)
    - Pattern Comparison
    - Letter Comparison
    - Complex Reaction Time Test (CRT)
  - **Executive Functioning (Fluid)**
    - Trails B
    - CLOX
  - **Memory/Attention (Fluid)**
    - WMS-III Spatial Span
    - WMS-III Digit Span
  - **Psychomotor Ability (Fluid)**
    - Finger Tapping Test
    - Trails A
    - WAIS Digit Symbol Copy and Substitution
  - **General Intelligence (Crystalized)**
    - WRAT



Useful Field of View®

- The Useful Field of View® is defined as the area from which one can extract visual information in a single glance without eye or head movement. While it is a test of visual attention, it is also sensitive to visual impairment.
- A measure of visual speed of processing.

Okonkwo, O. C., Wadley, V. G., Ball, K. K., Vance, D. E., & Crowe, M. G. (2008). Dissociations in visual attention deficits among persons with Mild Cognitive Impairment: Evidence and implications. Aging, Neuropsychology, and Cognition, 15(4), 492-505. DOI: 10.1080/13825580701844414; PMID: 18584341; PMCID: PMC18584341

Welcome to UFOV Test 1

This exercise will measure how fast you can identify a single object.

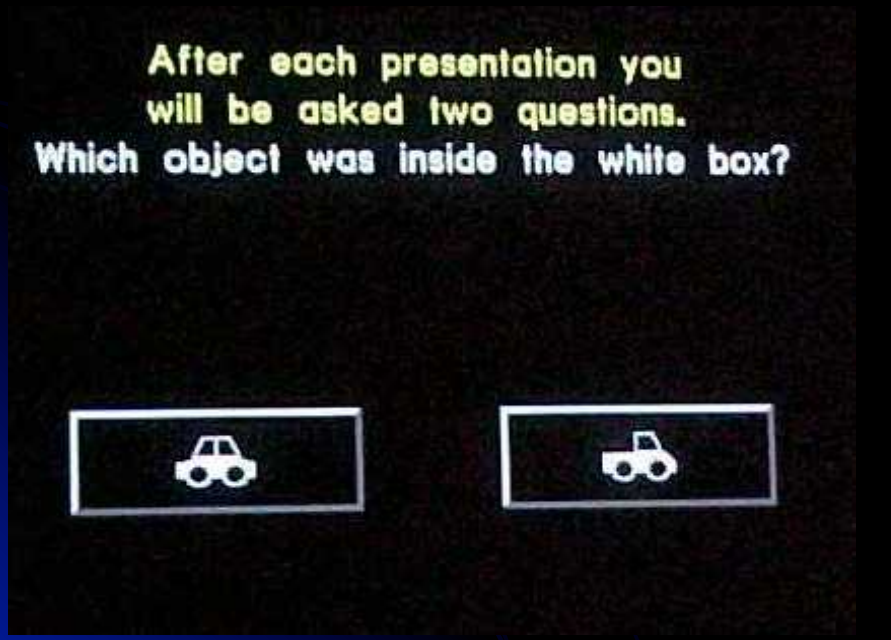
Touch continue for a demonstration

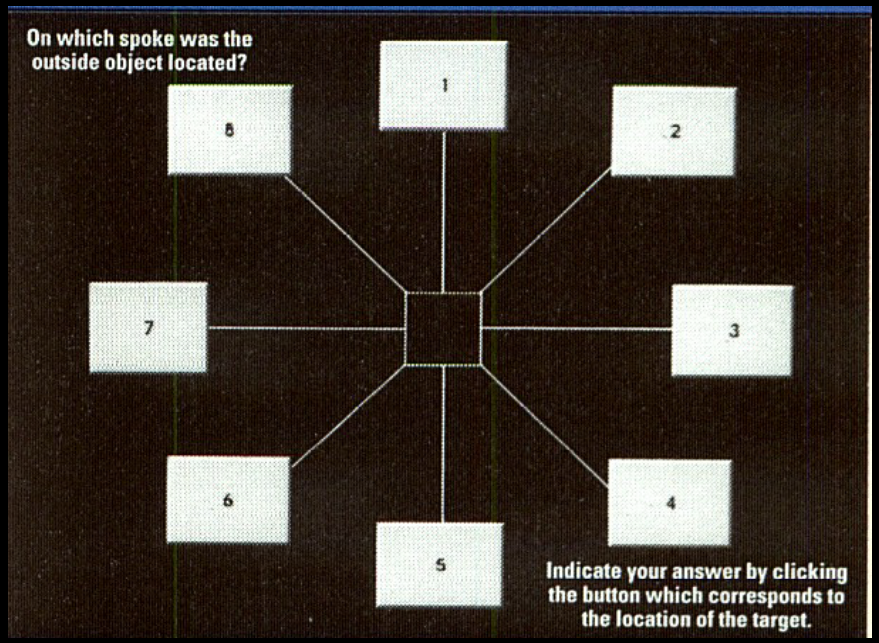
Which object was inside the white box?

Welcome to UFOV Test 2

This exercise will measure how fast you can divide your attention between two objects.

Touch continue for a demonstration

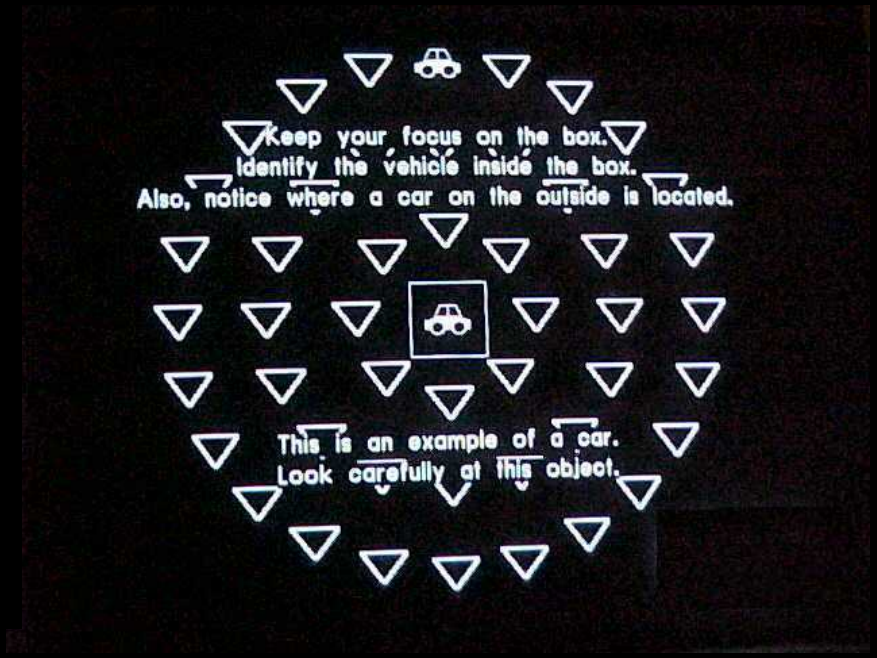


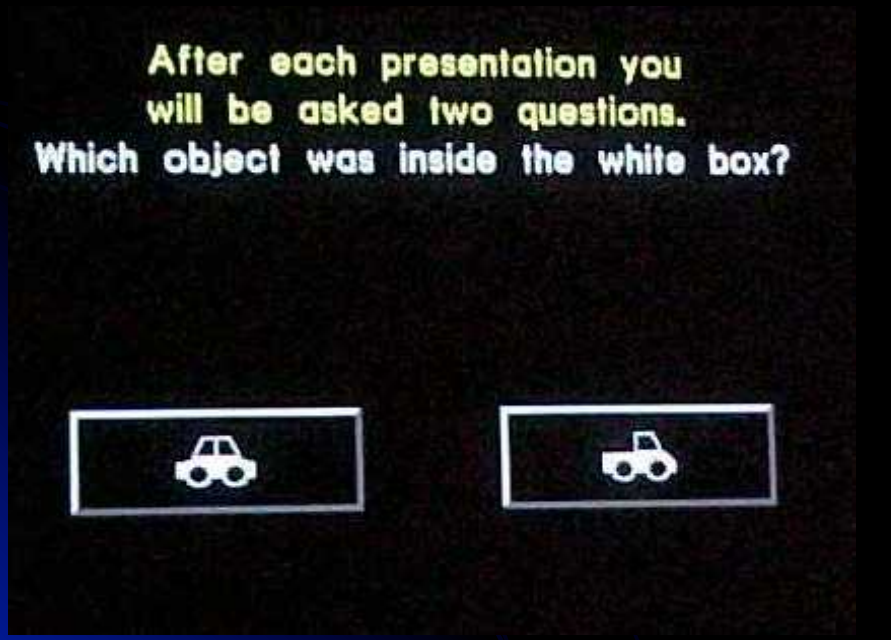


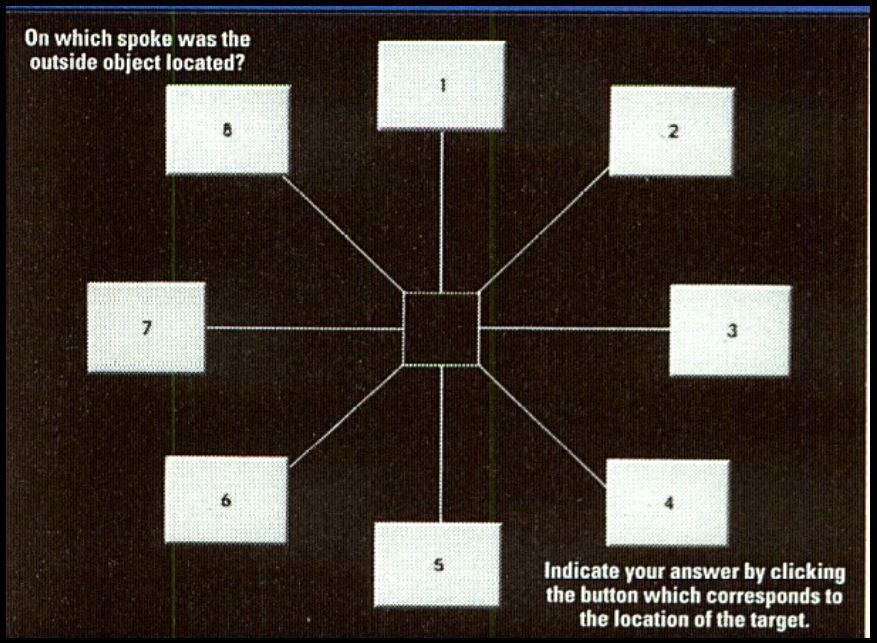
Welcome to UFOV Test 3

This exercise will measure how fast you can divide your attention between two objects when the outside object is surrounded by clutter.

Touch continue for a demonstration



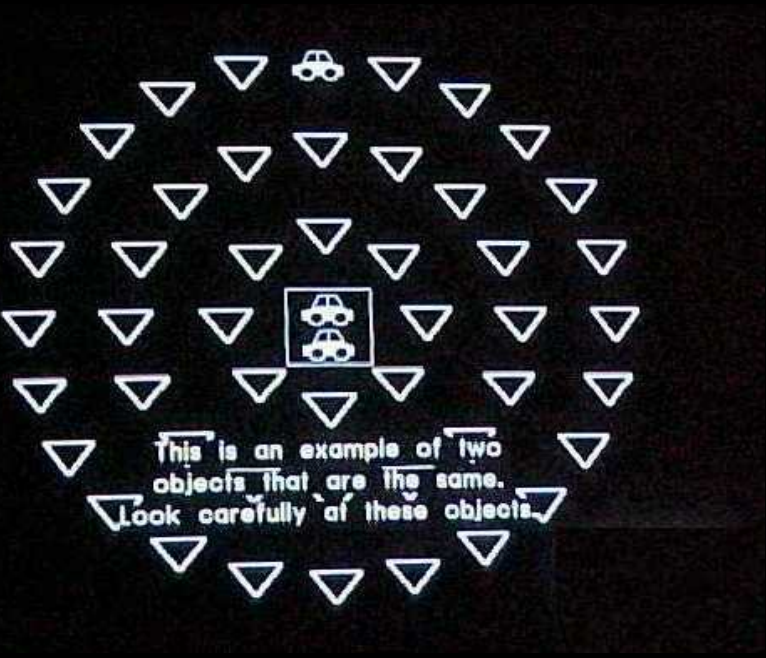


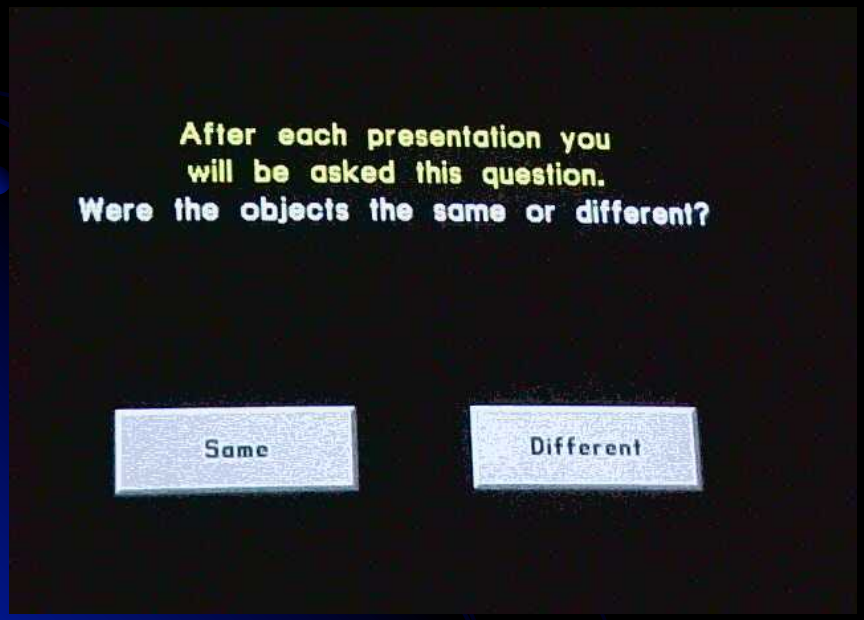


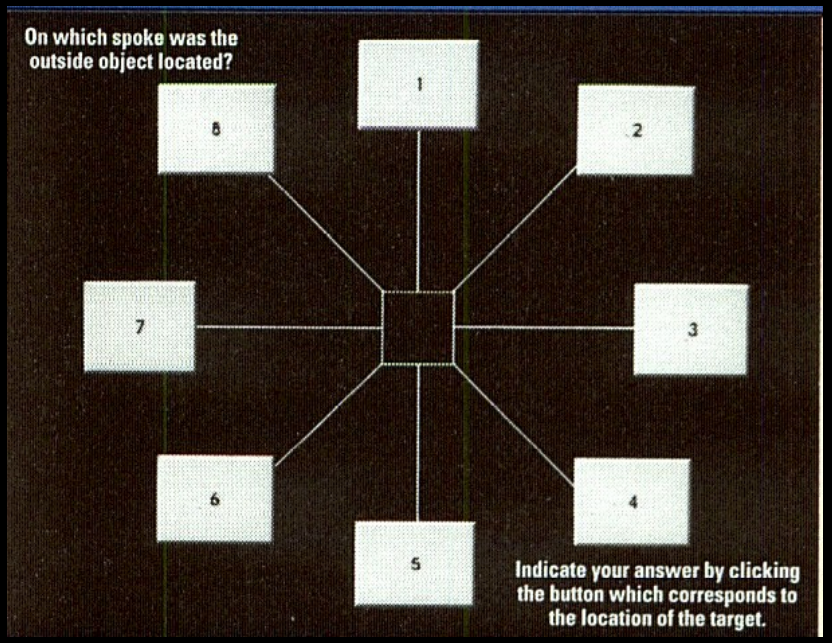
Welcome to UFOV Test 4

This exercise will be like the previous exercise except the center task will be more difficult.

Touch continue for a demonstration

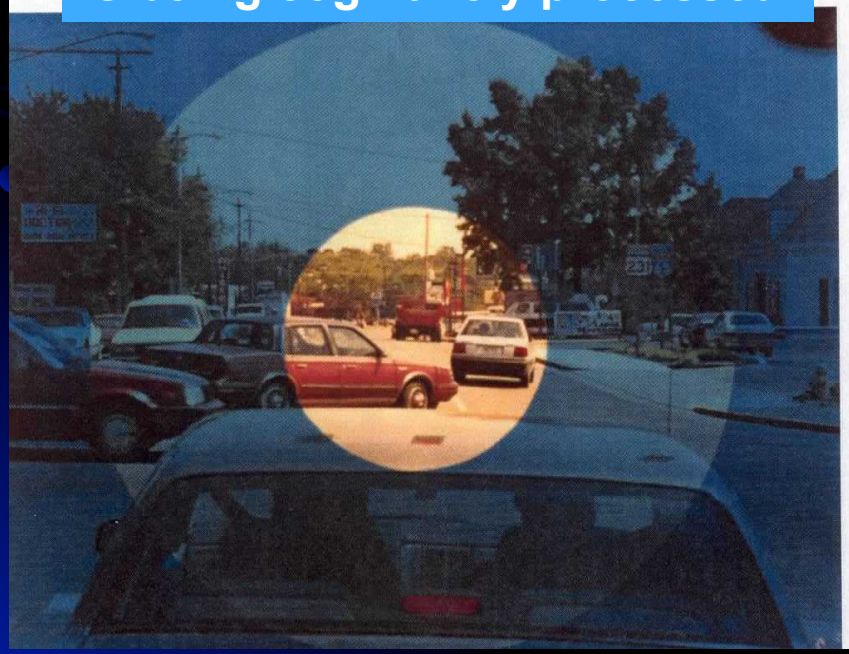




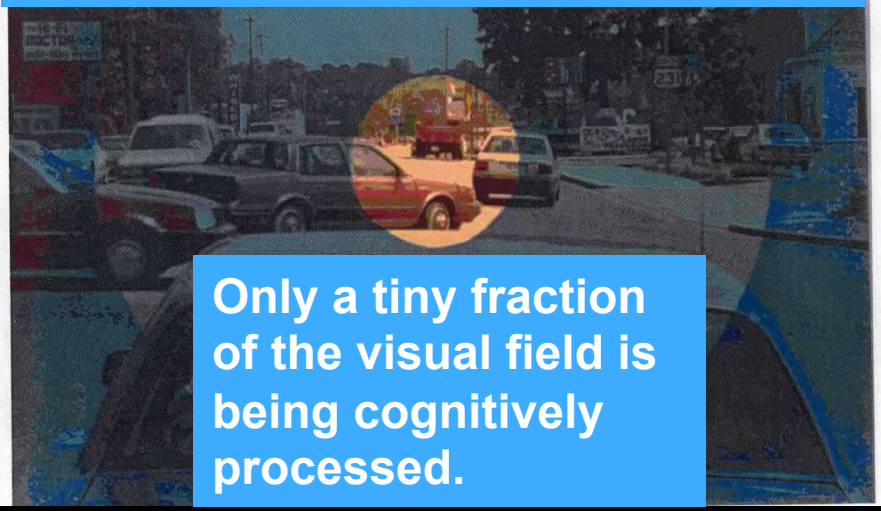


GOOD UFOV – Can see more information at a moment's glance.

Wider view is better! This means more of the visual field is being cognitively processed.



POOR UFOV – Can see little information at a moment's glance. Could compromise driving?



Only a tiny fraction of the visual field is being cognitively processed.

DRIVING SIMULATOR used in this study.

HIV Driving Simulator Study (N = 26)

- Older age was associated with lower divided attention reaction time in the simulator.
- Poor UFOV performance was predictive of slower reaction time, number of pedestrians hit, and driving outside of the lane.
- Poor UFOV test performance was related to higher self-reported accidents in the past year.

Vance, D. E., Fazeli, P. L., Ball, D. A., Slater, L. Z., & Ross, L. A. (2014). Cognitive functioning and driving simulator performance in middle-aged and older adults with HIV. Journal of the Association of Nurses in AIDS Care, 25(2), e11-e26. DOI: 10.1016/j.jana.2013.12.001; PMID: 24513104; PMCID: PMC3939674

BEHAVIORAL COGNITIVE INTERVENTIONS

Cognitive Training/Braining Training

Cognitive Training/Brain Training computerized programs target to improve a variety of cognitive domains.

- Meta-Analysis of 52 Computerized Cognitive Training Studies (Lampit et al., 2014)

- Treatment/effect sizes varied widely by domain and by amount of training/dosage.
  - Verbal memory (g = .08)
  - Working memory (g = .22)
  - Nonverbal memory (g = .24)
  - Visuospatial skills (g = .30)
  - Speed of processing (g = .31)
  - Attention (g = non-significant)
  - Executive functioning (g = non-significant)

Speed of Processing Training

- This speed of processing training protocol has been used to improve the rate at which normal, community-dwelling older adults process information (Vance, Dawson, Wadley, Edwards, Roenker, Rizzo, & Ball, 2007).
- It has been shown to improve driving performance and measures of everyday functioning (i.e., The ACTIVE Study; The Accelerate Study).
- Because of its efficacy in older adults, speed of processing training may improve such performance in adults with HIV.

Vance, D. E., Fazeli, P. L., Ross, L. A., Wadley, V., & Ball, K. (2012). The effects of speed of processing training on middle-aged and older adults with HIV. *Journal of the Association of Nurses in AIDS Care, 23*(6), 500-510.

ACTIVE Studies

HIV ISSUES	SOP TRAINING BENEFITS
Decreased Speed of Processing	Improved Speed of Processing
Poorer Driving	Improved Driving
Poorer IADL Performance	Improved IADL Performance
Decreased Locus of Control	Improved Locus of Control
Risk for Depression	Protection against Depression
Poorer Self-rated Health	Improved Self-rated Health
Poorer Health-related Quality of Life	Improved Health-related Quality of Life

Vance, D. E., Humphrey, S. C., Nicholson, W. C., & Jablonski-Jaudon, R. (2014). Can speed of processing training ameliorate depressive symptomatology in adults with HIV? *Annals of Depression and Anxiety, 1*(3), 4.

Methods

Speed of Processing Training

Baseline

No-Contact Control

Posttest

R03

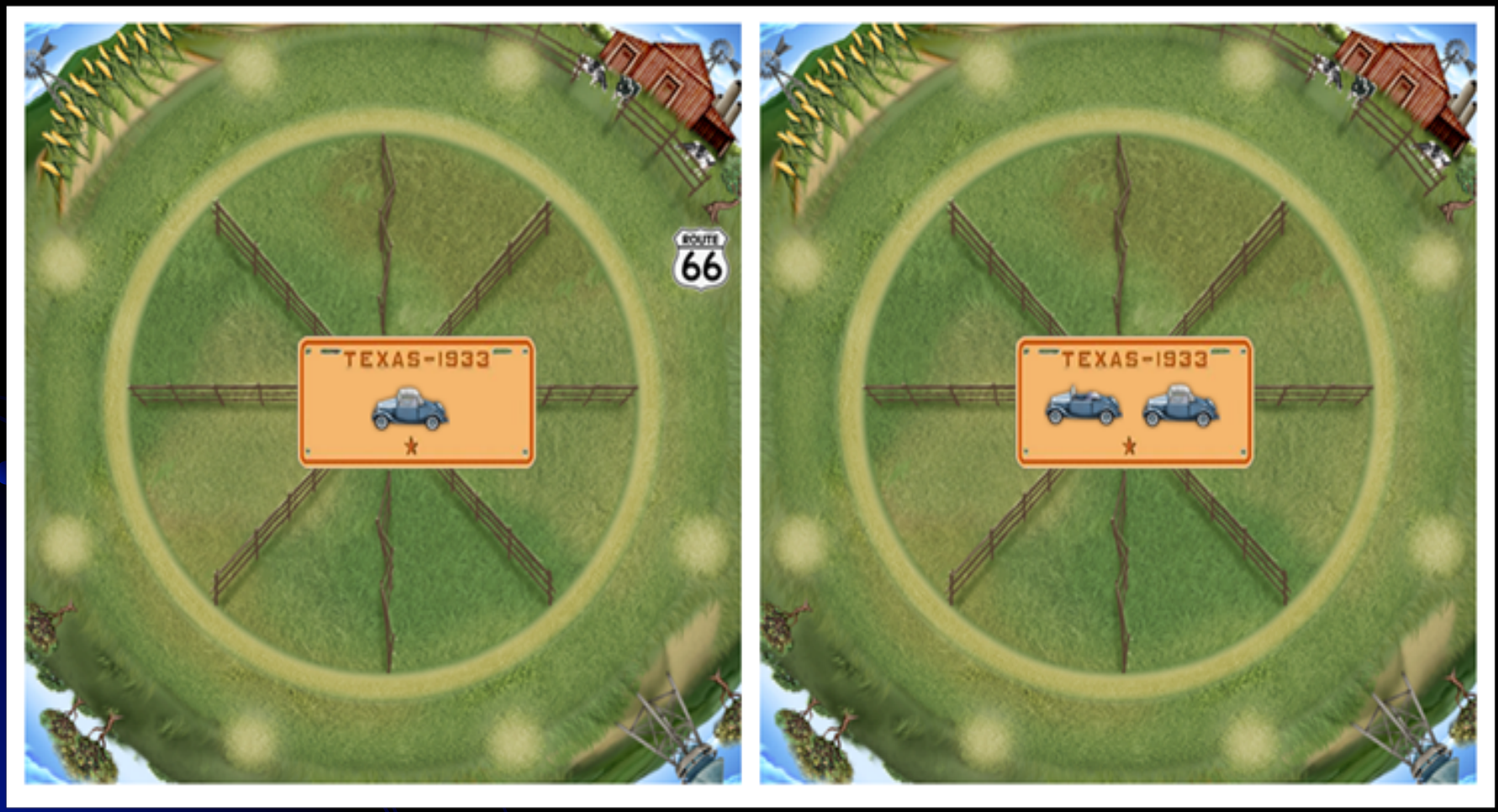
CCTS Study

Neuropsychological & Everyday Functioning Measures (5-6 weeks apart)

Variable	No-Contact Control Group (*n* = 24)		Speed of Processing Group (*n* = 22)	
	n (%)	Mean *(SD)*	*n* (%)	Mean *(SD)*
Age		52.88 (7.71)		50.11 (6.88)
Gender				
Male	17 (70.8%)		17 (77.3%)	
Female	7 (29.2%)		5 (22.7%)	
Race/Ethnicity				
Caucasian	12 (50.0%)		15 (68.2%)	
African American	12 (50.0%)		7 (31.8%)	
Education (years)		13.13 (2.88)		13.32 (2.10)
Household Income ($10K)		2.04 (1.63)		1.77 (1.51)
Years Diagnosed with HIV		16.30 (6.83)		13.01 (8.12)
HIV Viral Load (copies/mL)		1,936.78 (6,544.28)		8,357.86 (18,911.48)
Current CD4+ T Lymphocyte Count/mm^3		433.75 (220.09)		471.27 (291.73)

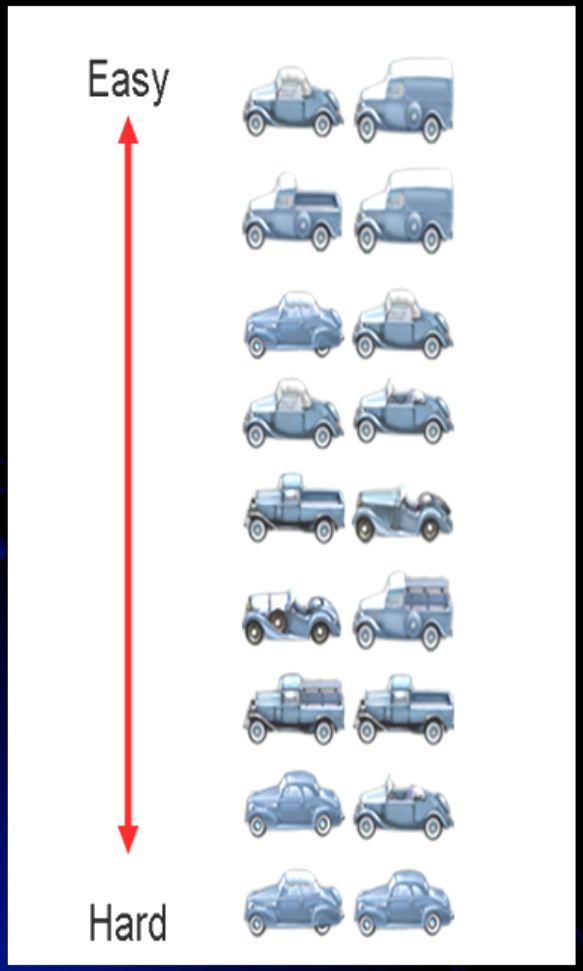
Methods

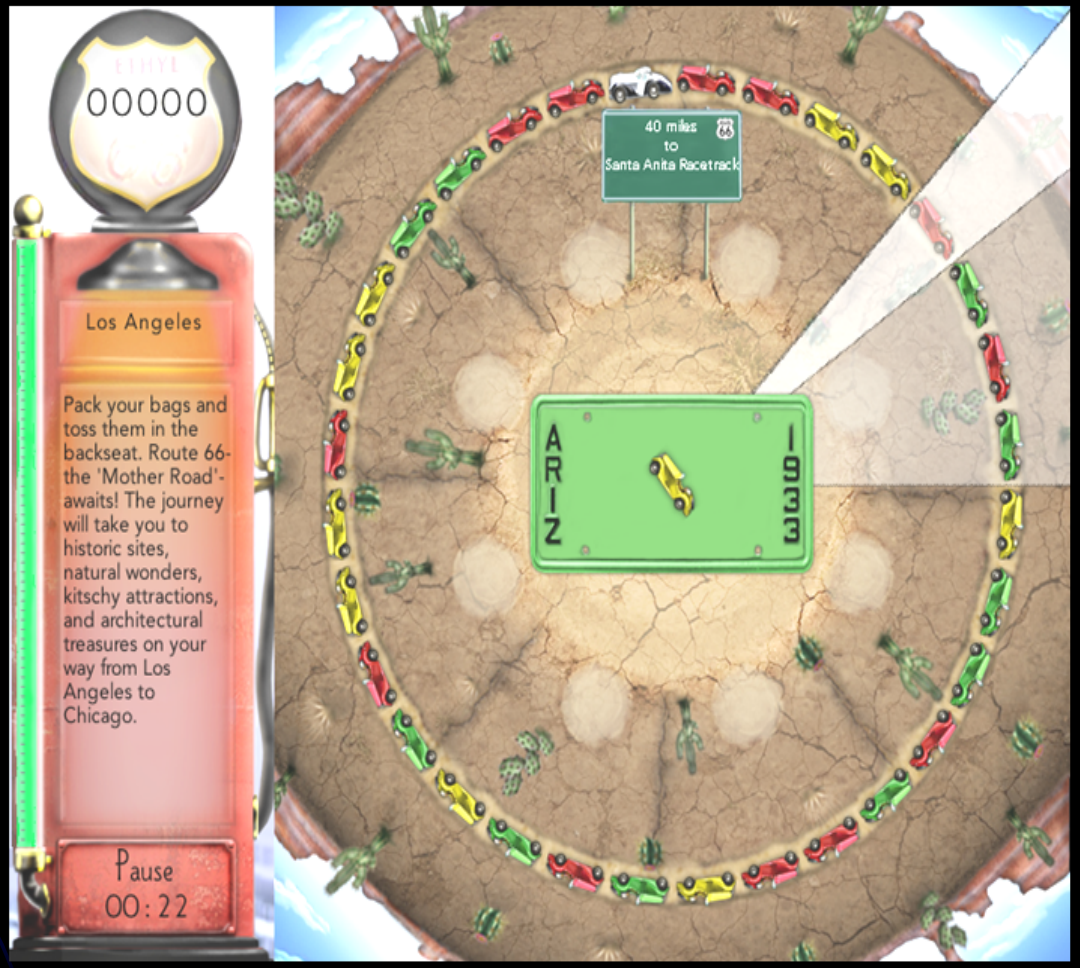
- Speed of Processing Training



Methods

- Speed of Processing Training (continued)





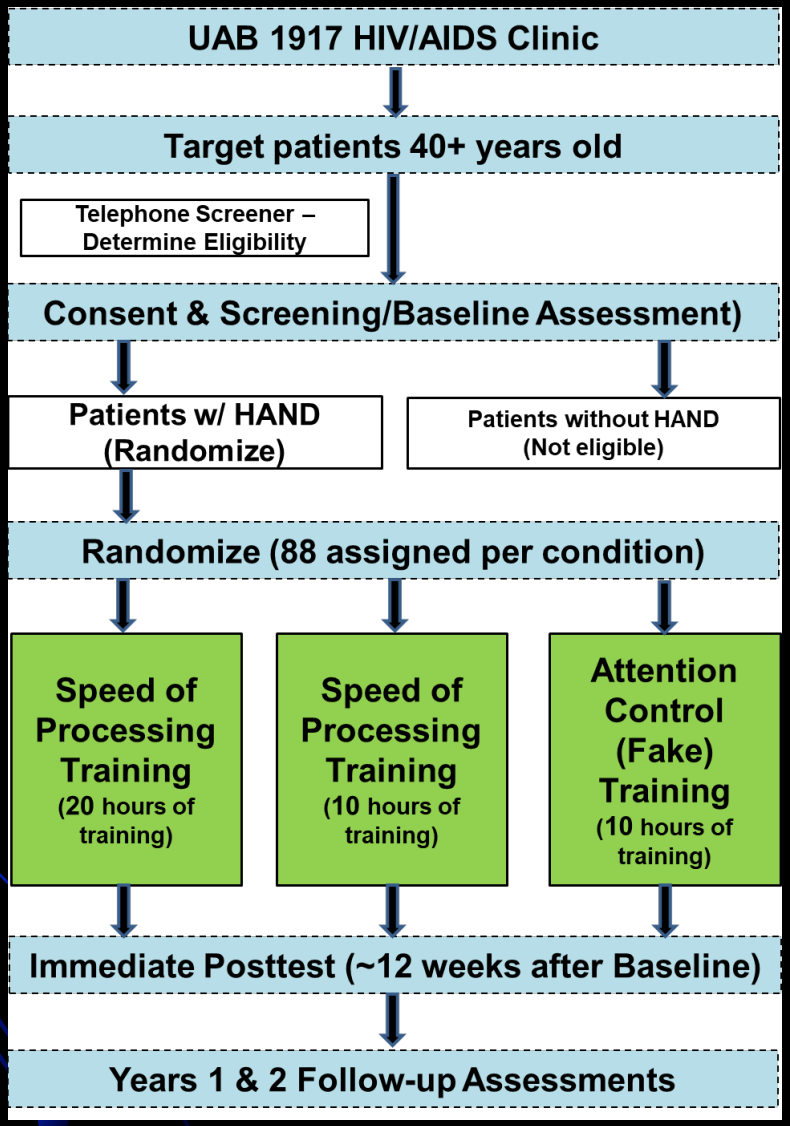
Pre and Post UFOV Scores for Training Groups

	Pre-Training	Post-Training
SOP Training	740	509.75
Control	890.09	753.75

CURRENT STUDY

Driving Simulation assessed at Baseline, Posttest, Year 1, and Year 2

Retrospective and Prospective Accident Reports will be gathered from the Division of Motor Vehicles.



This study may improve speed of processing in middle-aged and older adults with HIV which may improve driving safety as well as reduce the incidence of HIV-Associated Neurocognitive Disorder (HAND).

NIH/NIMH – "An RCT of Speed of Processing Training in Middle-Aged and Older Adults with HIV" (1R01MH106366-01 A1 – VANCE, PI)

Vance, D., Fazeli, P., Shacka, J., Nicholson, W., McKie, P., Raper, J., Azuero, A., Wadley, V., & Ball, K. (2017). Testing a computerized cognitive training protocol in adults aging with HIV-associated neurocognitive disorder: An RCT in the Southern United States. Journal of Medical Internet Research: Research Protocols.6(4), e68.

Case Study from THINKFAST

A simple qualitative comparison was completed between baseline and post-test.

Frascati Criteria CR	Case A 10 hrs of Internet Training	Case B 10 hours of SOP Training	Case C 20 hours of SOP Training	Comparisons/ Observations
CR Baseline	5	5	5	Case C no longer has HAND.
CR Posttest	5	5	4	
CR Improvement	0	0	-1	
UFOV® Baseline	667	1,084	1,031	Cases B & C improved the most.
UFOV® Posttest	480	634	248	
UFOV® Improvement	-177	-450	-783	

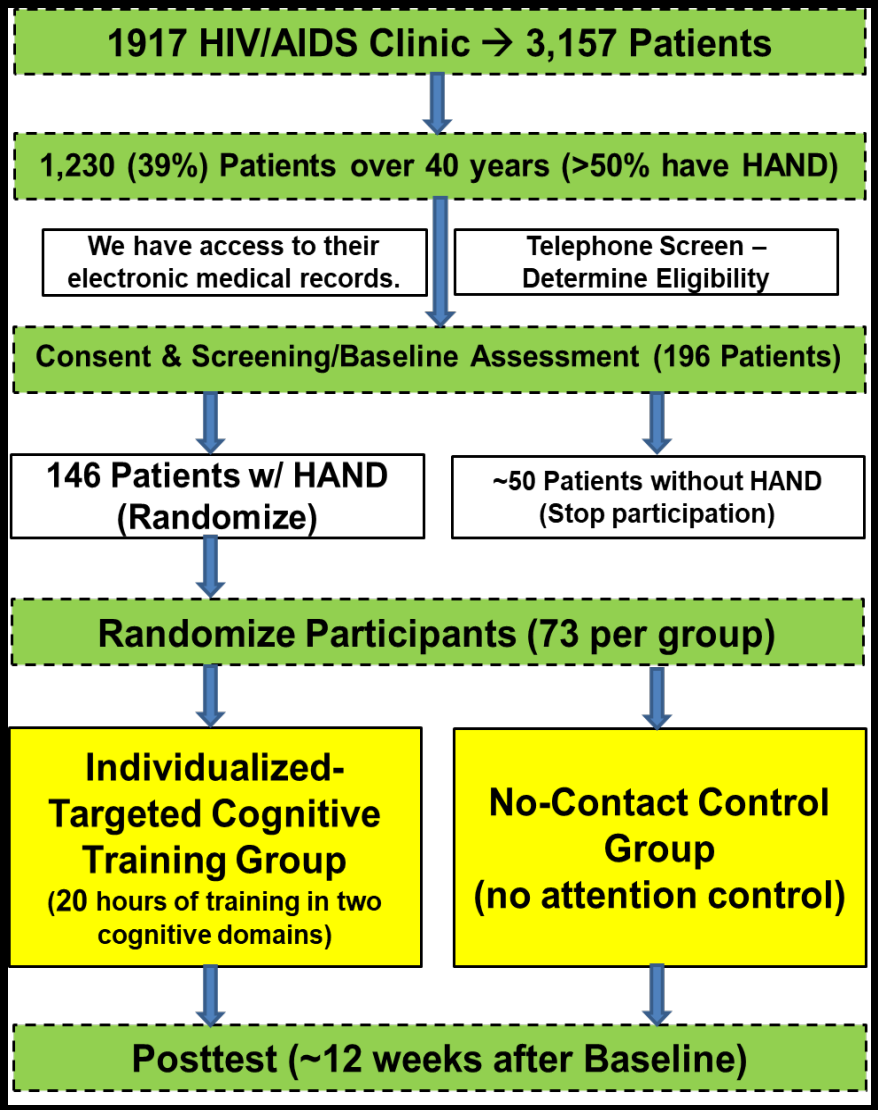
Note. CR = Clinical Rating; HAND = HIV-Associated Neurocognitive Disorder; hrs = hours; SOP = Speed of Processing; UFOV® = Useful Field of View.

Hossain, S., Fazeli, P. L., Tende, F., Bradley, B., McKie, P., & Vance, D. E. (2017). The potential of computerized cognitive training on HIV-associated neurocognitive disorder: A case comparison study. Journal of the Association of Nurses in AIDS Care, 28(6), 971-976. DOI: 10.1016/j.jana.2017.06.011

THE TRAINING ON PURPOSE STUDY (TOPS)

Thus, a hierarchy based upon Wicken's Model of Information Processing and the Diminished Speed of Processing Theory is used to determine the areas in which cognitive training will be administered.

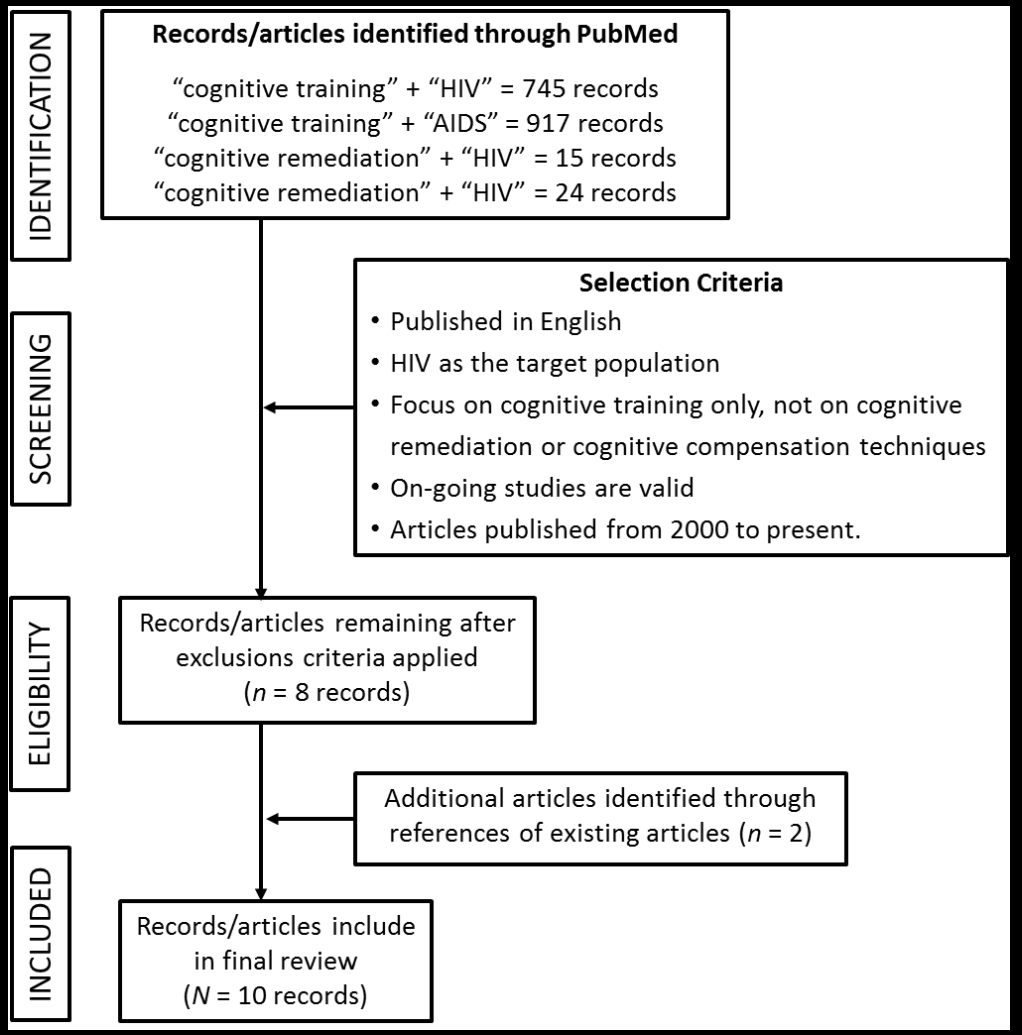
According to Wicken's Model of Information Processing, attentional processes underlie other basic cognitive processes including memory, executive functioning, psychomotor functioning, et cetera, and thus should be primary candidates for remediation.



NIH/NINR R21-award (Vance, PI: 1R21NR016632-01) titled: "Individualized-Targeted Cognitive Training in Older Adults with HAND".

Cognitive Training in HIV Adults

- For the most part, cognitive training programs have shown improvement in domains in which training was targeted.
- Targeted areas of training varied ranging from speed of processing, attention, and memory.
- Improvement in overall cognitive functioning is not well established.



Vance, D. E., Fazeli, P. L., Cheatwood, J., Nicholson, C., Morrison, S., & Moneyham, L. (in press). Computerized cognitive training for the neurocognitive complications of HIV infection: A systematic review. Journal of the Association of Nurses in AIDS Care.

Aerobic Exercise on Cognitive Function

- **Goal:** To investigate the effects of a 16-week aerobic exercise intervention on cognitive function in people with HIV.
- 13 PLWH attending the out-patient clinics who did not have a known cognitive impairment, between 18 and 65 years.
- 2 Groups
  - **Exercise Group** (*n* = 5) completed a 16-week aerobic exercise program training, 3 times per week (2 supervised sessions and one unsupervised session).
  - **Control Group** (*n* = 6) received no intervention.
- Although the findings indicated a strong association between higher levels of exercise capacity and higher levels of cognitive function, 16 weeks of aerobic exercise did not significantly improve cognition.

McDermott et al. (2017). The effects of a 16-week aerobic exercise programme on cognitive function in people living with HIV. *AIDS Care, 29*(6), 667-674.

ENGAGMENT

- Engagement – Physical Exercise, Social, Mental Activity
  - 139 Adults with HIV (M_{age} = 48.7 years; 48% 50+)
  - Cross-sectional → Active Lifestyle & Neuropsychological Testing
  - Physical Exercise – Any strenuous exercise in the past 72 hours?
    - No (0)/Yes (1)
  - Social Engagement – Lawton and Brody ADL Questionnaire
    - "Frequently engage in or initiate social activity"
    - No (0)/Yes (1)
  - Mental Activity – Working full- or part-time?
    - No (0)/Yes (1)
  - Active Lifestyle Factors (ALF) ranged from 0 to 3
  - "**Increasing number of ALFs was associated with a lower prevalence of HAND** [df = 1, X^2 = 5.1, p = .02)."
    - **ALF 0 – 63% HAND** (34% ANI, 18% MND, 11% HAD)
    - ALF 1 – 51% HAND (35% ANI, 14% MND, 2% HAD)
    - ALF 2 – 33% HAND (27% ANI, 3% MND, 3% HAD)
    - **ALF 3 – 20% HAND** (15% ANI, 5% MND, 0% HAD)

Fazeli, P. L., Woods, S. P., Heaton, R. K., Umlauf, A., Couaux, B., Rosario, D., …The HNRP Group (2014). An active lifestyle is associated with better neurocognitive functioning in adults living with HIV infection. *Journal of Neurovirology.* DOI: 10.1007/s13365-014-0240-z

Multidomain Cognitive Interventions

The Agewell Trial (Clare et al., 2015, *BMC Psychiatry*)

- **<u>Goal:</u> To change lifestyle factors to support successful cognitive aging and avoid dementia.**
- 75 community-dwelling adults 50+ years old
- 3 Groups
  - **Control** (n = 27)
  - **Goal Setting** (n = 24)
  - **Goal Setting with Mentoring** (n = 24)
- Goal setting focused on behavioral goals to improve health, nutrition, as well as cognitive, physical, and social activities to support neuroplasticity
- Assessed over 12 months
- Those in the goal setting groups improved on measures of executive functioning, memory, aerobic activity, cholesterol measures, balance, agility, flexibility, and grip strength.
- Similar studies are being conducted as well to reduce the risk of Alzheimer's disease (Anstey et al., 2013, *Trials*).

MEDICAL COGNITIVE INTERVENTIONS

Combination Antiretroviral Therapy (cART)

- cART protects cognitive functioning by helping to reconstitute the immune system and by decreasing the effects of HIV on the brain, which is a viral reservoir.
  - Al-Kindi et al. (2011) reviewed 23 studies and found that ART was associated with modest improvements in motor function, attention, and executive function.
    - Albeit, limited improvements on verbal memory, visual memory, visuospatial function, and language.
    - **↑ cognitive performance → ↑ CD4 counts**

TREATMENT OF COMORBIDITIES

Variable	18-29 (*n* = 138)	30-39 (*n* = 343)	40-49 (*n* = 623)	50-59 (*n* = 301)	60+ (*n* = 73)	*p*-value
Viral Load	41,905 (160,660)	59,829 (183,677)	28,603 (144,991)	26,788 (119,793)	21,896 (120,304)	**.018**
Non-dectectable Viral Load (<50c/mL)	50 **(36.2%)**	135 (39.4%)	354 (56.8%)	197 (65.4%)	56 **(76.7%)**	**.000**
CD4+ Lymphocyte Count	451 (272)	420 (264)	460 (299)	479 (290)	470 (287)	.113
Number of Prescribed Medications*	**7.43** (7.06)	10.22 (7.81)	11.72 (8.17)	12.48 (7.95)	**14.82** (7.32)	**.000**
Number of Medical Conditions (co-morbidity)**	**2.20** (1.73)	2.89 (1.93)	3.96 (2.27)	4.40 (2.21)	**4.52** (1.90)	**.000**

Increased prevalence of comorbidities with HIV

- **Coronary Artery Disease**
- **Renal Disease**
- **Diabetes**
- **Hypertension**
- **Hypercholesterolemia**

Vance, D. E., Mugavero, M., Willig, J., Raper, J. L., & Saag, M. S. (2011). Aging with HIV: A cross-sectional study of co-morbidity prevalence and clinical characteristics across decades of life. Journal of the Association of Nurses in AIDS Care, 22(1), 17-25.

TREATMENT OF MOOD DISORDERS

- In a sample of 1,478 adults with HIV, **~40%** experience depression and **~20%** experience anxiety (Vance, Mugavero et al., 2011).
- **Hypothalamus-Pituitary-Adrenal (HPA) Axis** → Stress increases cortisol which can produce neuroinflammation over time (Satori et al., 2012).
- Adults with HIV with **higher levels of depression** were more likely to report forgetfulness and cognitive problems and tended to over-report cognitive problems (Thames et al., 2011).

TREATMENT OF SUBSTANCE ABUSE DISORDERS

- Results suggest that some cognitive function (partially) recover after sustained abstinence.
- Methampthetamine (Iudicello et al., 2011, doi: 10.1080/13803390935412637)
- Cocaine (Inozemtseva et al., 2016, doi:10.1080/10826084.2016.1178293)
- Polysubstance Abuse (Schmidt et al., 2017, doi: 10.1080/13803395.2016.1196165)

Psychostimulants

- **Methlyphenidate (Ritalin®)** is a psychostimulant dopamine agonist.
  - Finding are mixed (e.g., small sample size, poor adherence).
  - In a single-blind cross-over, placebo-controlled study (*N* = 10), those with more depression and cognitive slowing at baseline **experienced better cognitive functioning** on computer measures of dual-task reaction time and choice (Hinkin et al., 2001).
  - ↑ cognition in MS (Harel et al., 2009) & normal adults (Tomasi et al., 2011).
  - Treatment of Fatigue (maybe increases attention/arousal)
  - ↓ total cholesterol, LDL, and triglycerides (Charach et al., 2009).
  - Psychostimulants can be abused (Volkow & Swanson, 2008).
- **Modafinil –** Used to improve wakefulness and attention.
  - Results are mixed…
  - Pre-post experimental design over 4-weeks.
  - Modafinil Group (*n* = 59) & Placebo-control Group (*n* = 44)
    - 40% with a history of drug use
    - 29% taking antidepressants
    - 20% with hepatitis C
  - Modafinil Group
  - **↑ Global cognitive functioning**
  - **↓ Cognitive Failures Questionnaire**

MEDICATIONS

- **Serontonin Reuptake Inhibitors** (i.e., trazodone, citalopram, sertraline) Of 658 adults of HIV,
  - 71% used ART
  - 30% used SRIs
  - 10% used statins
  - Undetectable CSF viral load more likely for those who used SRIs.
  - **Significant improvement on cognitive testing** for those prescribed SRIs (Letendre et al., 2007).

- **Transdermal Selegiline** – a monoamine oxidase inhibitor used to treat depression.
  - Mixed results
  - In a placebo-controlled, double-blind study of 14 adults with HIV over 10 weeks
    - ↑ verbal memory & psychomotor abilities (Sacktor et al., 2001).
  - In a large sample (*N* = 128) with neural damage confirmed by MRS, **no differences observed between groups** (placebo/ active) at both 3- and 6-months (Schifitto et al., 2009).

MEDICATIONS

- **Lithium –** may help decrease oxidative stress and inflammation.
  - In vitro study suggests it may be **neuroprotective in HIV** (Everall et al., 2002).
  - In a single-arm study of 21 adults with HIV, **improvement in global cognitive** functioning was observed (Letendre et al., 2006).
  - In a sample of 8 cognitively-impaired adults with HIV, **improvements in global deficit scores,** particularly in speed of processing and executive function domains, were observed in all participants 12 weeks after receiving low-dose titrated lithium. Mood, measured by the Beck Inventory scores, did not change (Letendre et al., 2006).
  - Albeit, it is not without risks (e.g., gastrointestinal disturbances, tremor, hypothyroidism, renal dysfunction) and can adversely interact with other medications (e.g., nonsteroidal anti-inflammatories, thiazide diuretics).

MEDICATIONS

- **Hormone Replacement Therapy**
  - **ESTROGEN** – A meta-analysis of 36 randomized trials, Hogervorst and Bandelow (2010) concluded ERT was not effective in improving cognition.
  - Dye et al. (2012) – A review of studies suggests that 17B-estradiol may be neuroprotective against Alzheimer's disease and improve cognitive; but it is unknown for adults with HIV.
  - **TESTOSTERONE** – Treatment for cognitive problems has not been well established either (Mitsiades et al., 2008).
    - Is used for treatment of muscle wasting and weight loss (Choi et al., 2005).
    - Increases risk for prostate cancer, liver disease, hyperviscosity, erythrocytosis, prostatic hypertrophy, & sleep apnea (Bassil & Morley, 2010).

COGNITIVE COMPENSATION

Nick.ms

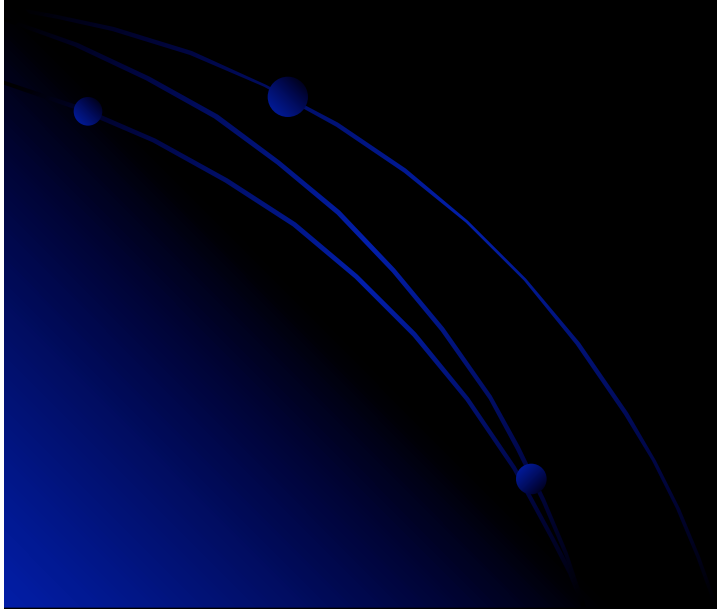
Suggests and Compensation Strategies by Nick

- **Low-Tech Suggestions**
  - **Medication Adherence –** Weekly pill box
  - **Redundancies** – Keys, medications, etc.
  - **Journaling** – Keeping track of events.
  - **Driving Down the Road –** "I would be driving down the highway and suddenly be unable to remember where I was going or why. I still knew who I was and where I was and what I was doing, but clueless as to why….it is a frightening experience."
    - Involved in 4 accidents in the two year prior to diagnosis which he was at-fault
    - SOLUTION 1 → Post-It goes on the Dashboard Stating. ..Destination
    - SOLUTION 2 → Slow down, plan A to B, be more careful.

- **High-Tech Suggestions**
  - **Evernote (evernote.com) & Wunderlist (wunderlist.com) –** For keeping track of lists and reminders.
  - **iCal –** The calendar that comes with the iPad.
  - **30/30 App –** "Sense of timing is off." It allows one to set a certain amount of time on a task, and then gives you an alert when time is up.
  - **Check App –** Helps him keep up with bills, credit cards, and bank accounts.

Vance, D. E., Nicholas, N., & Humphrey, S. C. (2015). HIV neurocognitive impairment and aging: Perspectives on neurocognitive reserve and behavioral remediation/compensation strategies. Austin Journal of Neuropsychiatry and Clinical Neurosciences, 1(1): 1002.

PARTING THOUGHTS



TAKE HOME POINTS

- ✓ Use it or loose it!
- ✓ That which is good for the body is good for the brain.
- ✓ Comorbidities, both physical and psychiatric, can impair cognition and cognitive reserve.
  - ✓ Thus, it is important to adhere to treatments to protect cognitive reserve.

TAKE HOME POINTS

- ✓ Encourage patients to continue to pursue interests, especially if they are cognitively challenging.
  - ✓ Ask patients what they are doing to protect brain health.
  - ✓ Empower patients to be proactive about brain health.
  - ✓ The activity needs to make the brain sweat!!!
  - ✓ Start early to protect and preserve brain function.
- ✓ Be on the lookout for new therapeutic strategies (e.g., brain fitness programs, tDCS)
- ✓ Compensation strategies are available.

Is Donepezil effective in improving cognition in adults with HIV? Yes…No…Maybe?

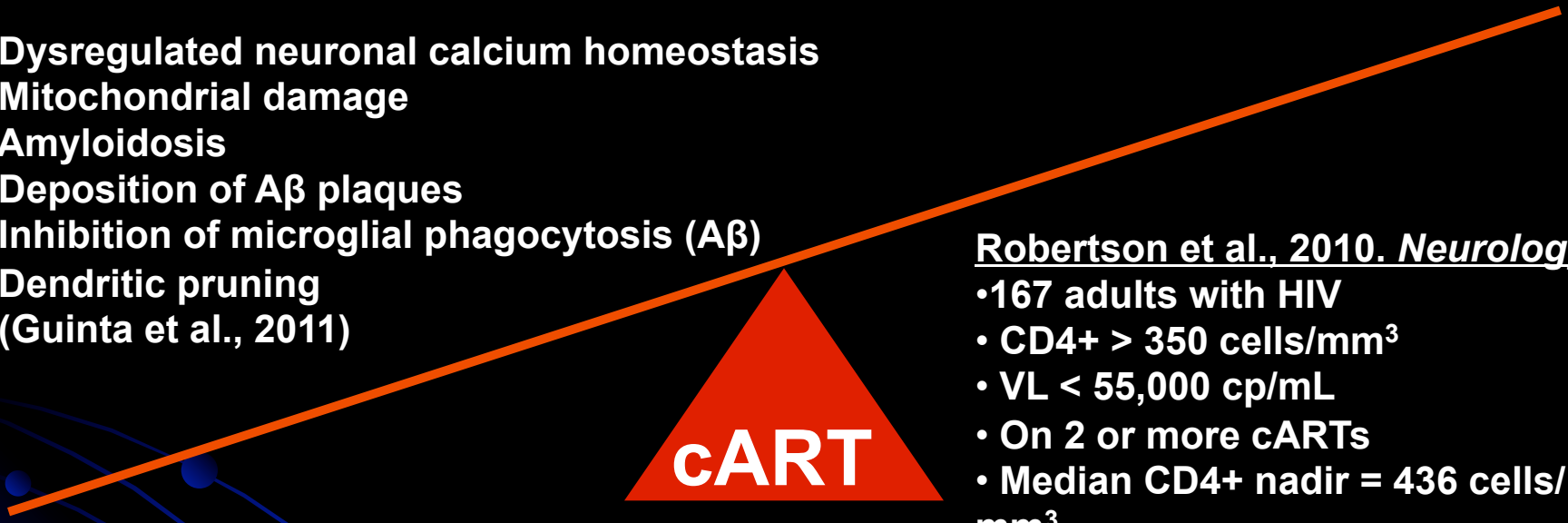
- **Acetylcholinesterase Inhibitors** (e.g., donepezil)
  - Yesavage et al. (2008) used donepezil and cognitive training over a 1-year period in 168 nondemented, normal community-dwelling older adults with memory complaints.
  - Pre-post design 2- group (placebo vs donepezil) where both groups received a cognitive training intervention
  - Donepezil produced the **same level of cognitive gains as placebo.**

- **Memantine –** Used in Alzheimer's disease to target the glutamatergic system (i.e., NMDA receptors) and reduce neuronal excitotoxicity; also functions as an agonist on dopamine D_2 receptor.
  - Memantine **reduced hippocampal damage** in an HIV encephalitis rodent model (Anderson et al., 2004).
  - In a pre-post, randomized, double blind, placebo-controlled study of memantine in 140 adults with AIDS Dementia Complex, **no significant improvements** in neurocognitive performance were observed between baseline and week 16 among those who received the drug or the placebo (Schifitto et al., 2007).

Balancing the Effects of cART Toxicity

- ↓ Neuroinflammation caused HIV
- ↓ Decrease HIV encephalopathy
- Keeps HIV from progressing to AIDS

- Dysregulated neuronal calcium homeostasis
- Mitochondrial damage
- Amyloidosis
- Deposition of Aβ plaques
- Inhibition of microglial phagocytosis (Aβ)
- Dendritic pruning
- (Guinta et al., 2011)



Robertson et al., 2010. *Neurology.*

- 167 adults with HIV
- CD4+ > 350 cells/mm^3
- VL < 55,000 cp/mL
- On 2 or more cARTs
- Median CD4+ nadir = 436 cells/mm^3
- Participants were taken off of cART and monitored cognitively over 96 weeks.
- **Their mean cognitive scores significantly improved from weeks 24, 48, 72, and 96.**

Follow up to the MOCA

If the results from the MOCA or other cognitive screeners suggest cognitive decline, further steps can be taken including:

1) talking with the patient further about such cognitive concerns;

2) referring them to a psychologist or neurologist;

3) seeking underlying causes of cognitive decline (e.g., depression);

4) then, the patient is monitored over time for improvement or progression of such cognitive symptoms.

Vance, D. E., Farr, K., & Struzick, T. C. (2008). Assessing the clinical value of cognitive appraisal in adults aging with HIV. Journal of Gerontological Nursing, 34(1), 36-41.

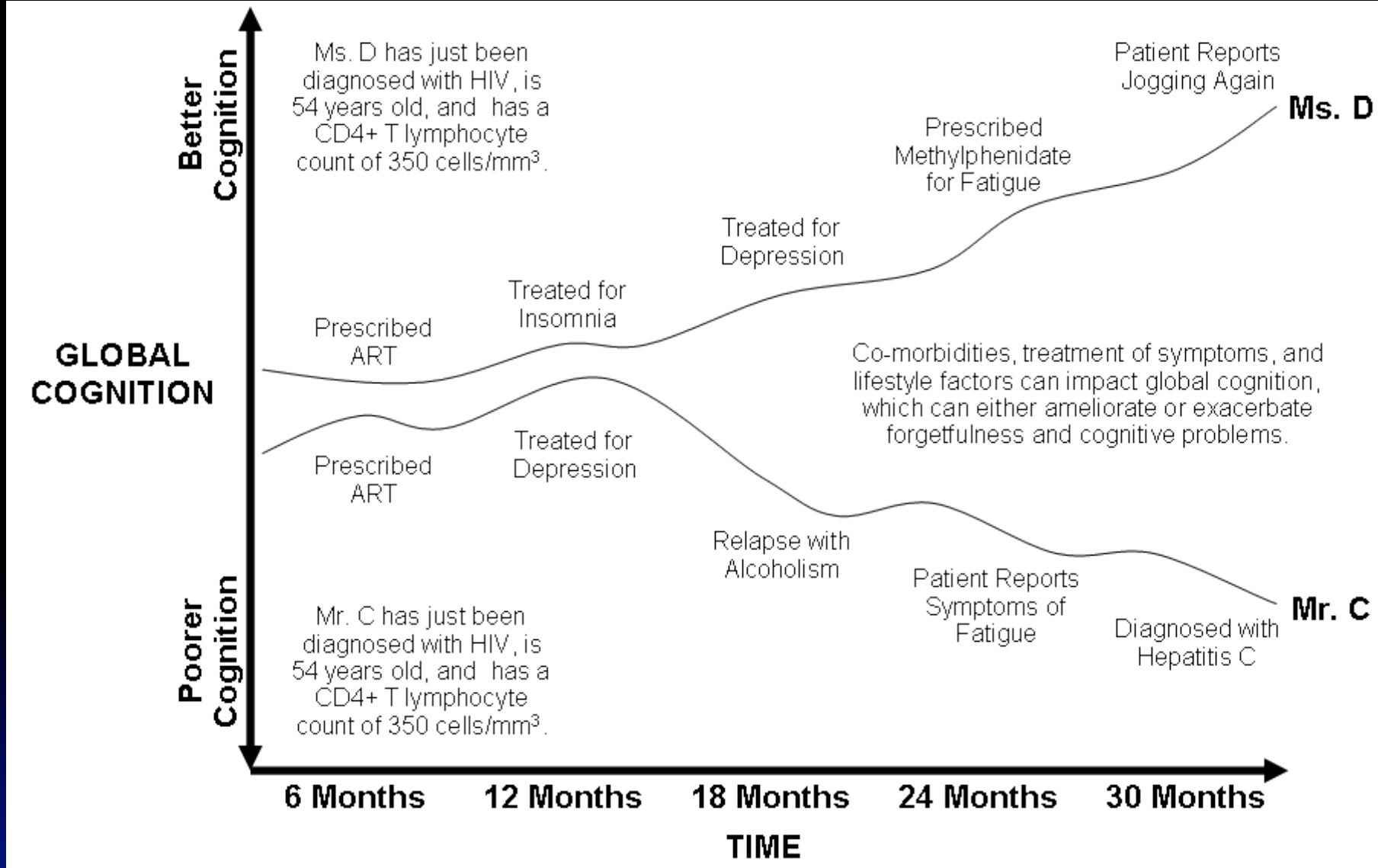
PHYSICAL EXERCISE & HIV gp120

- HIV gp120 impairs neurogenesis.
- Using a gp120 transgenic mouse models, Lee and colleagues (2013) allowed mice to run.
  - **Exercise increased:**
    - Neural progenitor cell proliferation in the hippocampal dentate gyrus
    - Survival rate and generation of newborn cells
    - Normalized dendritic outgrowth of neurons
    - Hippocampal brain-derived neurotrophic factor (BDNF) expression
    - Normalized hyperactivation of cyclin-dependent kinases 5 (dysregulation is involved in neurodegenerative diseases)
  - Unfortunately, **the positive effects on the brain reversed in lieu of detraining (no exercise).**

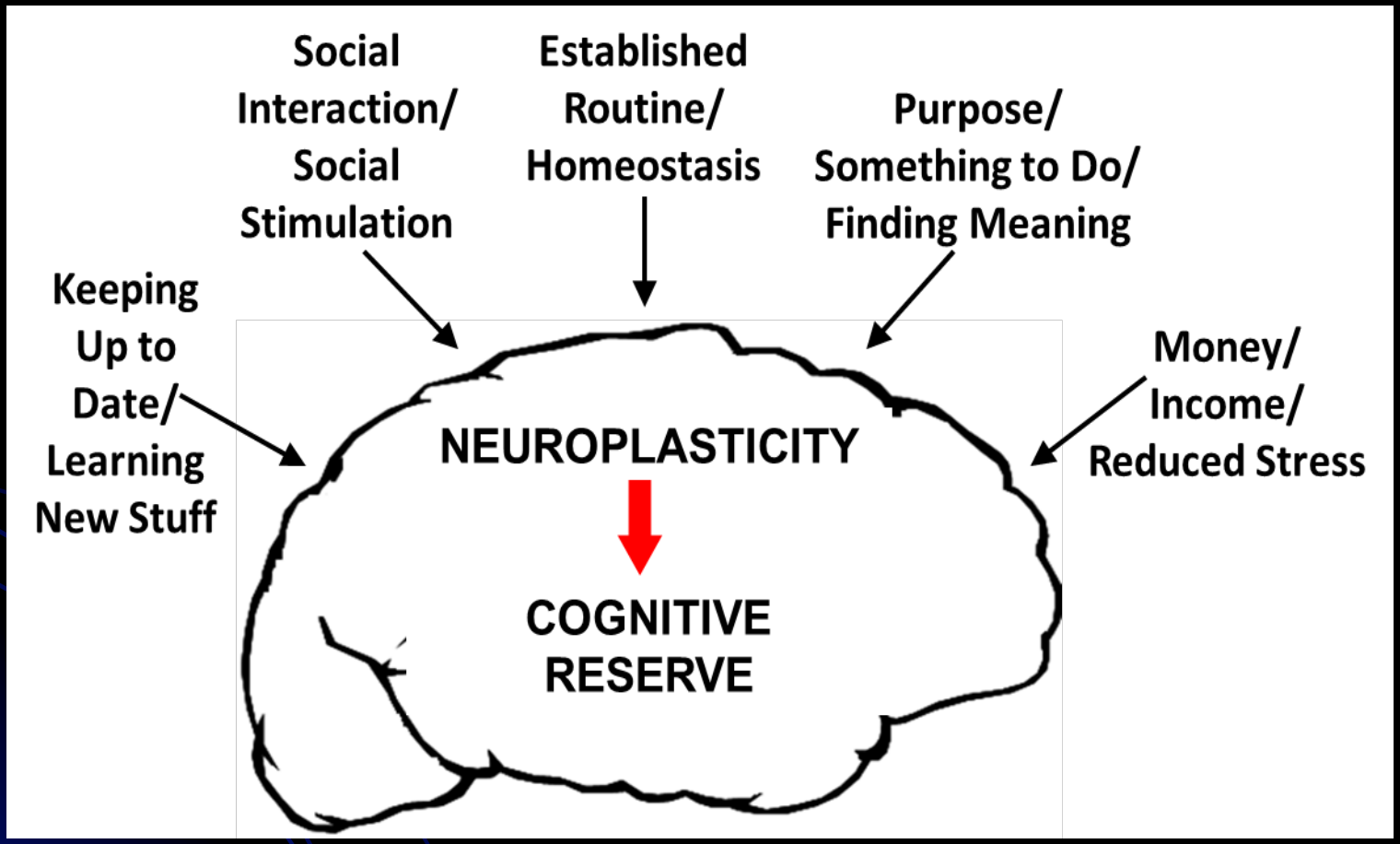
Lee, M. H., Amin, N. D., Venkatesan, A., Wang, T., Tyagi, R., Pant, H. C., & Nath, A. (2013). Impaired neurogenesis and neurite outgrowth in an HIV-gp120 trangenic model is reversed by exercise via BNDF prouction and Cdk5 regulation. *Journal of Neurovirology, 19*(5), 418-431.
DOI:10.1007/s13365-013-0194-6

SOP Training at Home

- Humphrey, S. C., Fazeli, P. L., & Vance, D. E. (2015). Feasibility of a home-based speed of processing training program in middle-aged and older adults with HIV. *Journal of Neuroscience Nursing,* 47(4), 247-254.
  - Within-subjects pre-post experimental design
  - 20 middle-aged and older adults (i.e., age 40+)
  - ~10 hours of training over 5-6 weeks
  - Significant improvements on the Useful Field of View (UFOV®) and TIADL Test
  - SOP can successfully be used in one's home.


Better Cognition
Poorer Cognition
GLOBAL COGNITION
Ms. D has just been diagnosed with HIV, is 54 years old, and has a CD4+ T lymphocyte count of 350 cells/mm3.
Prescribed ART
Treated for Insomnia
Treated for Depression
Prescribed Methylphenidate for Fatigue
Patient Reports Jogging Again
Ms. D
Co-morbidities, treatment of symptoms, and lifestyle factors can impact global cognition, which can either ameliorate or exacerbate forgetfulness and cognitive problems.
Mr. C has just been diagnosed with HIV, is 54 years old, and has a CD4+ T lymphocyte count of 350 cells/mm3.
Prescribed ART
Treated for Depression
Relapse with Alcoholism
Patient Reports Symptoms of Fatigue
Diagnosed with Hepatitis C
Mr. C
6 Months
12 Months
18 Months
24 Months
30 Months
TIME

According to one study, only 20% of adults with HIV were continuously employed over a 30-month period (Rabkin et al., 2004).



Vance, D. E., Humphrey, S. C., Yoo, M., Jones, G. D., & Nicholson, W. C. (2015). The role of employment on neurocognitive reserve in adults with HIV. *Journal of the Association of Nurses in AIDS Care, 26*, 316-329.

ENGAGEMENT

Older adults (*N* = 181) were randomly assigned to control and experimental groups.

Experimental group: attended 20 weekly social meetings during which they worked in teams to develop creative solutions to problems

Control group: did not attend any social meetings

- Compared to the control group, the experimental group who engaged in team problem-solving exhibited a positive change in neurocognitive ability from pretest to posttest.

- Areas of improvement observed in the experimental group were processing speed, inductive reasoning, and divergent thinking.

Stine-Morrow, E. A., Parisi, J. M., Morrow, D. G., & Park, D. C. (2008). The effects of an engaged lifestyle on cognitive vitality: A field experiment. *Psychology and Aging, 23*(4), 778-786. doi:10.1037/a0014341

COGNITIVE PRESCRIPTION
Jerry's Goals for the Week

LIFESTYLE FACTOR	DAILY/WEEKLY GOALS	October 1 – October 7
Physical Exercise	1. Go hiking for at least 30-minutes 2 times a week.	X X X X
	2. Do 10 push ups a day.	X X X X
Mental Exercise	1. Play the piano everyday for 20 minutes.	X X X
Nutrition	1. Take a multivitamin daily.	X X X X X X X
Social Engagement	1. Go out to dinner with a friend once a week.	X X
Mood Support	1. Take you antidepressant daily.	X X X X X X
Sleep Hygiene	No sleep problems	-----
Substance Use	No substance problems	-----

Vance, D. E., Eagerton, G., Harnish, B., McKie-Bell, P., & Fazeli, P. (2011). Cognitive prescription across the lifespan: A nursing approach to increasing cognitive reserve. *Journal of Gerontological Nursing, 37(4)*, 22-29. DOI: 10.3928/00989134-20101202-03

BACKGROUND

How many adults with HIV in the U.S. are 50 and older?

30%

40%

50%

70%

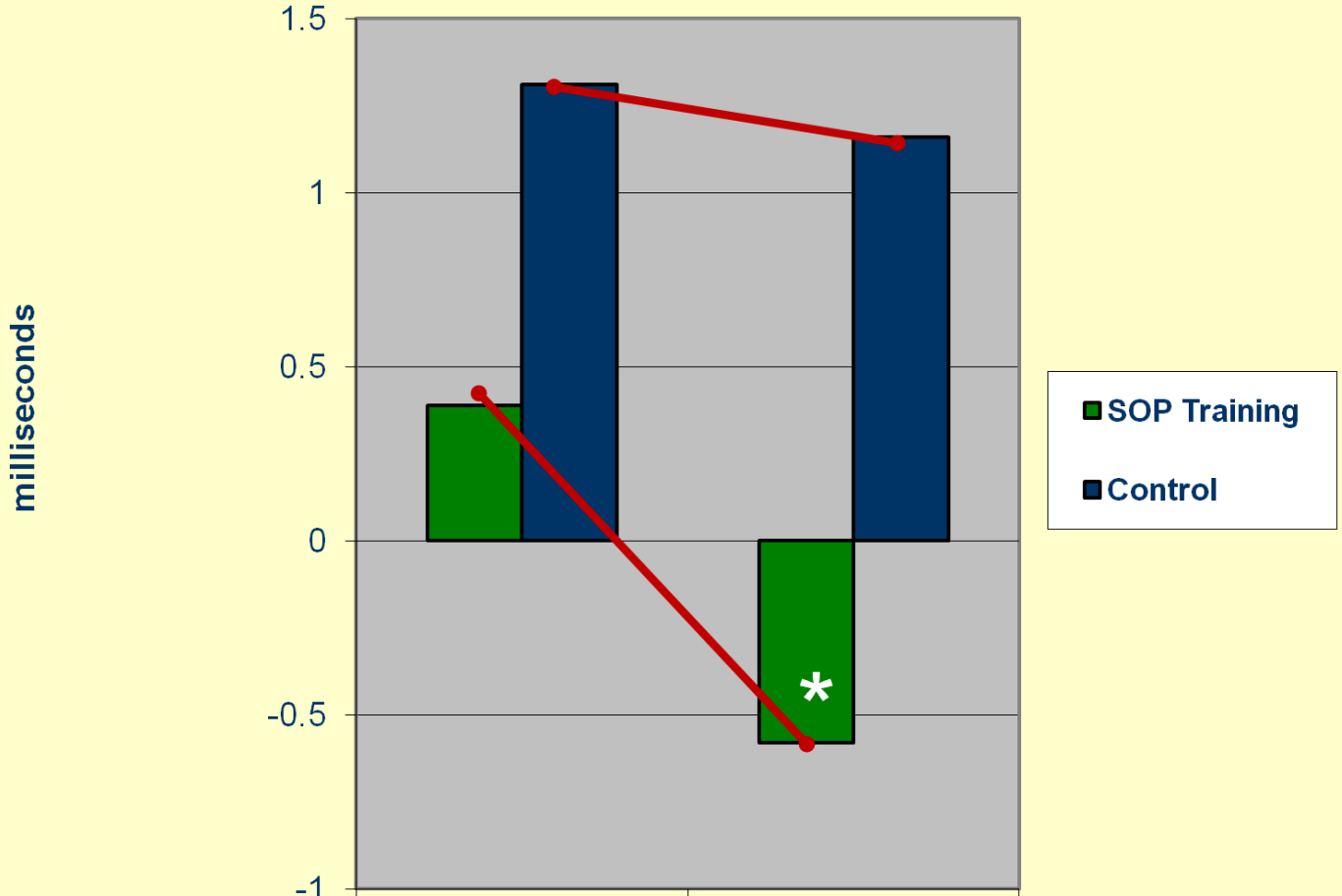
- By 2020, that number will rise to **70%.**

Is Successful Aging with HIV Possible?

SUCCESSFUL AGING	HIV
Length of Life	Compromised (?)
Biological Health	Compromised (?)
Mental Health	Depression, Anxiety
Cognitive Efficiency	Cognitive Decline (?)
Social Competence	Social Withdrawal
Productivity	Abandoned Goals
Personal Control	Loss of Control (?)
Life Satisfaction	Individual Differences

Vance, D. E., Bayless, H., Kempf, M. C., Keltner, N. L., & Fazeli, P. L. (2011). Aging, HIV, and wellness: Augmenting the components of successful aging. *Aging Health, 7*(3), 435-446.

Pre and Post TIADL Scores for Training Groups



	Pre-Training	Post-Training
SOP Training	0.39	-0.58
Control	1.31	1.16

MEDICATIONS

- **Transdermal Rivastigmine –** an acetylcholinesterase inhibitor used for mild/moderate Alzheimer's and Parkinson's disease..
  - Randomized-controlled pilot with 48-week follow-up of 76 adults with HIV with cognitive impairment (Muñoz-Moreno et al., 2017)
    - Transdermal rivastigmine (9.5 mg daily)
    - Lithium (400 mg twice daily)
    - Control (no new medication)
  - Although positive trends were found, no relevant changes observed in cognitive status observed between the groups.
  - Minor side effects detected in the two treatment groups.
  - Yet, in a MRI study in 17 aviremic adults with HIV, rivastigmine therapy was shown to reduce demyelination/axonal damage (Perrotta et al., 2017).
  - Therapeutic effects of rivastigmine are inconclusive.

PRESENTER DISCLOSURES

- * GRANTS/RESEARCH SUPPORT: NIH and University of Alabama at Birmingham – Grant support (e.g., 1R01MH106366-01A1; 1R21 NR16632-01; Women's Interagency HIV Study; etc…)

- * SPEAKER'S HONORARIA: Multidisciplinary Approaches across the Palliative Care Continuum Conference – Lecture Honorarium; Association of Nurses in AIDS Conference – Lecture Honorarium; International Antiretroviral Society – Lecture Honorarium; etc...

- * CONSULTING FEES: POSIT Science Inc. – Presenting their software as part of presentation; Department of Defense – Grant Reviewer; HIVERA Grant Reviewer, Berlin & Frankfort, Germany.

- * OTHER: Employee of the University of Alabama at Birmingham