26-27 May 2017

Barcelona, Catalonia, Spain

Measuring Cognitive Changes in HIV Infection: Size Really Matters

Jose A. Muñoz-Moreno, Ph.D.

Lluita contra la SIDA Foundation

Germans Trias i Pujol University Hospital

Badalona, Barcelona

Catalonia, Spain

Happy Birthday!

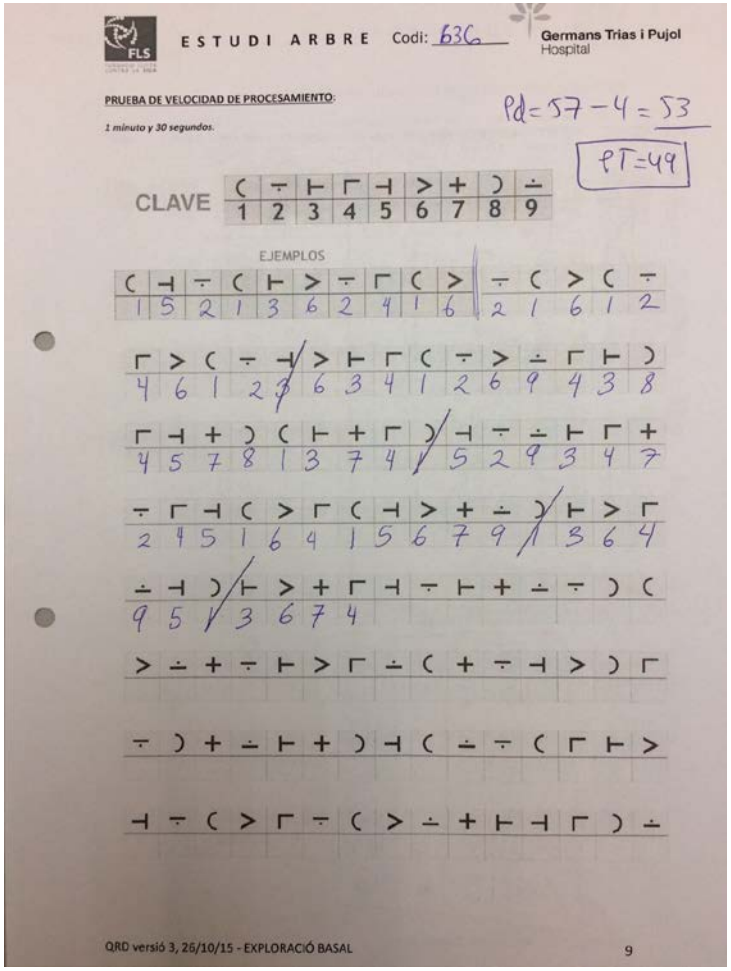
10th

International
Symposium on
Neuropsychiatry & HIV

FUNDACIÓ LLUITA CONTRA LA SIDA

Initial Examples

Information Processing Speed
SDMT (TEA Ediciones, 2002)


ESTUDI ARBRE Codi: 636

Germans Trias i Pujol Hospital

PRUEBA DE VELOCIDAD DE PROCESAMIENTO:

1 minuto y 30 segundos.

Pd=57−4=53

PT=49

CLAVE

1	2	3	4	5	6	7	8	9

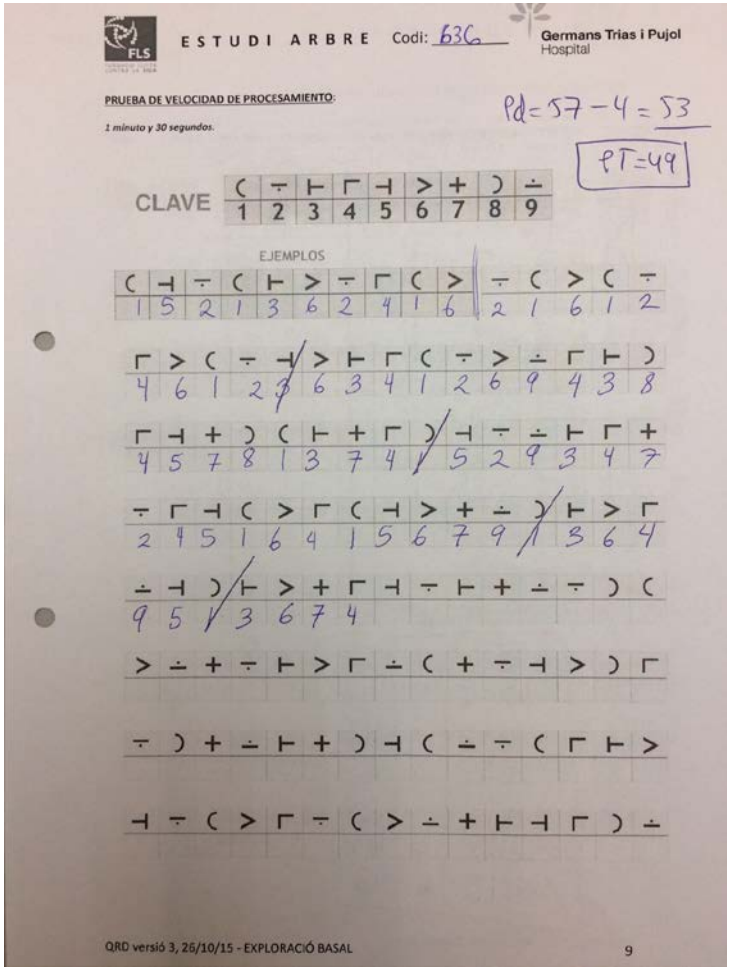
EJEMPLOS

QRD versió 3, 26/10/15 - EXPLORACIÓ BASAL 9

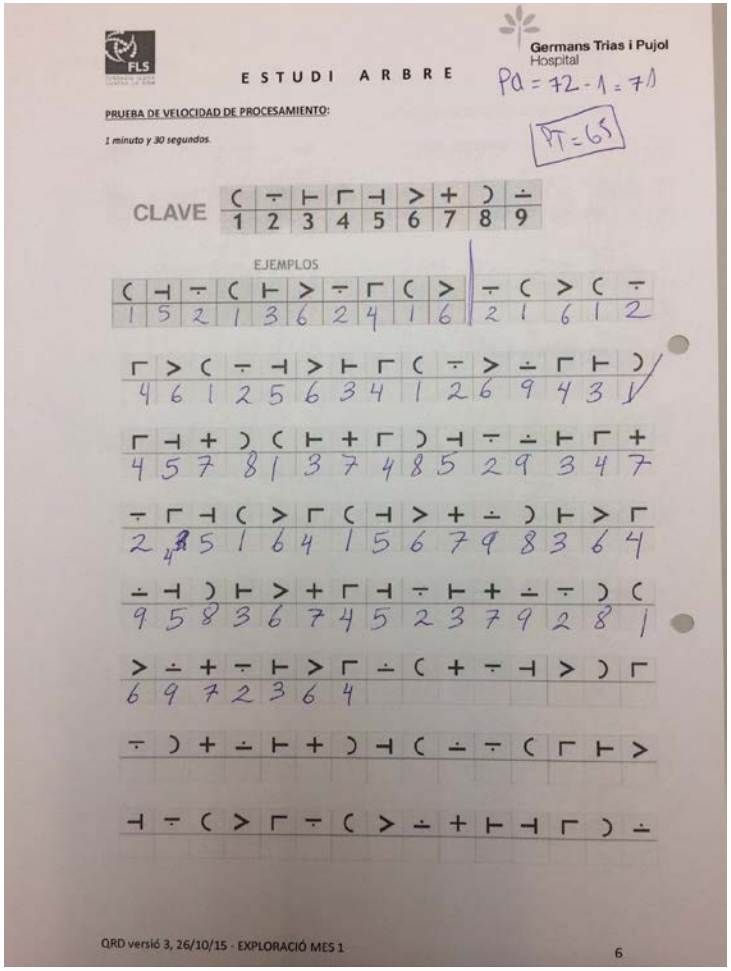
- *Raw score:* ***53***
- *T score:* ***49***
- *Z score:* ***-0.1***

Initial Examples

Information Processing Speed
SDMT (TEA Ediciones, 2002)



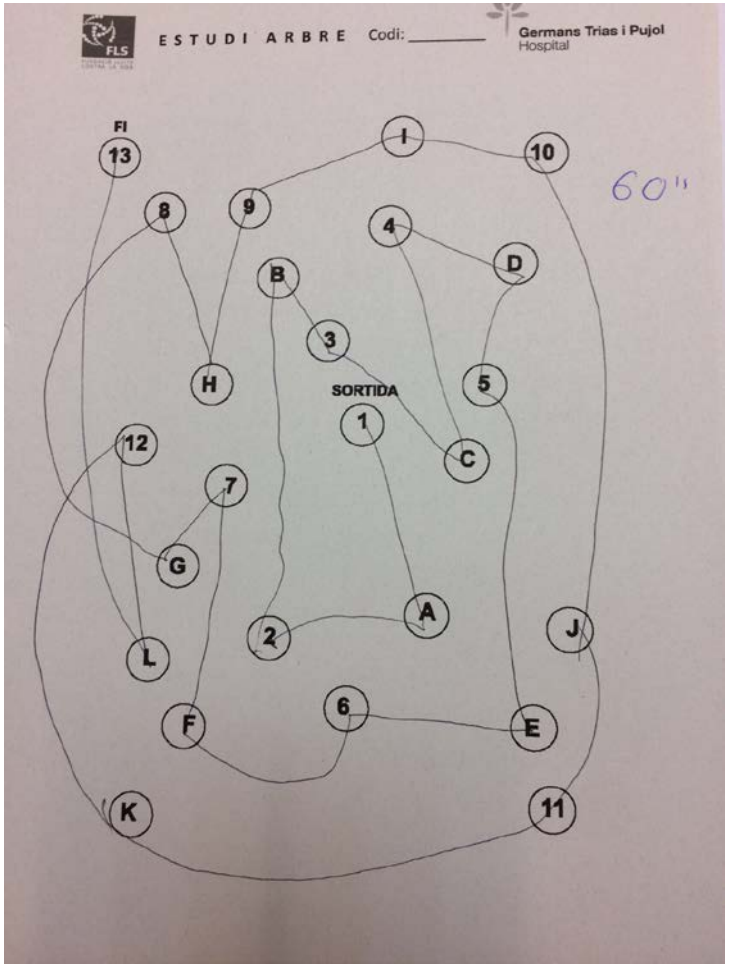
- *Raw score:* ***53***
- *T score:* ***49***
- *Z score:* ***-0.1***



- *Raw score:* ***71***
- *T score:* ***65***
- *Z score:* ***1.5***

Initial Examples

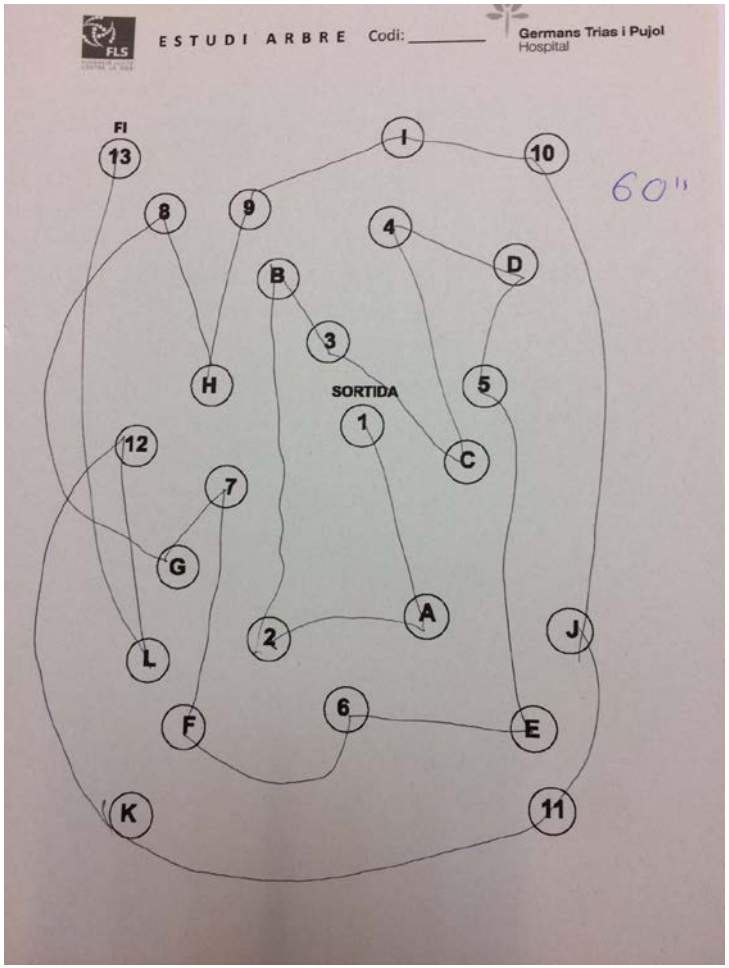
Executive Functioning
TMT-B (Periáñez JA, et al, 2007)



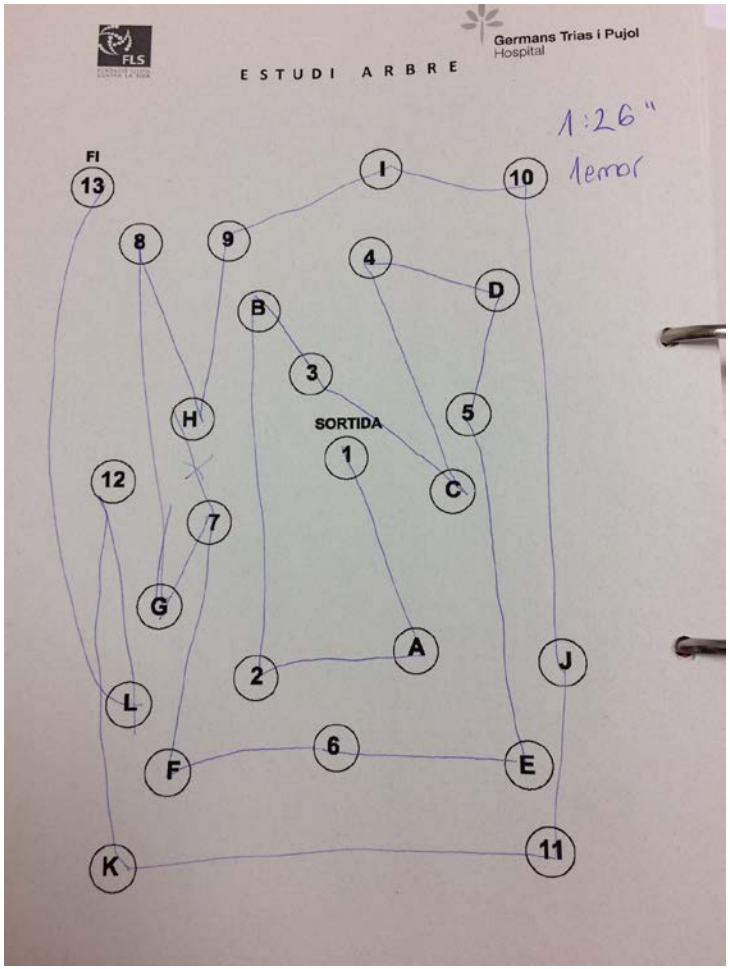
- *Raw score:* ***60***
- *T score:* ***46***
- *Z score:* ***-0.4***

Initial Examples

Executive Functioning
TMT-B (Periáñez JA, et al, 2007)



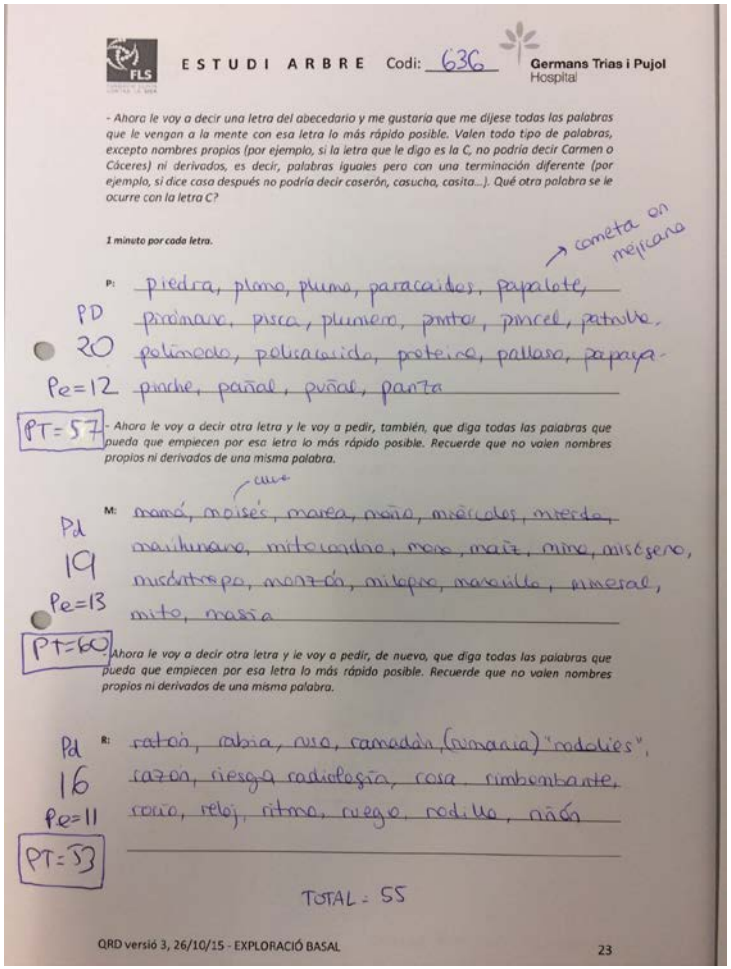
- *Raw score:* ***60***
- *T score:* ***46***
- *Z score:* ***-0.4***



- *Raw score:* ***86***
- *T score:* ***32***
- *Z score:* ***-1.8***

Initial Examples

Verbal Fluency
COWAT/PMR (Casals-Coll M, et al, 2013)



ESTUDI ARBRE Codi: 636

Germans Trias i Pujol Hospital

- Ahora le voy a decir una letra del abecedario y me gustaría que me dijese todas las palabras que le vengan a la mente con esa letra lo más rápido posible. Valen todo tipo de palabras, excepto nombres propios (por ejemplo, si la letra que le digo es la C, no podría decir Carmen o Cáceres) ni derivados, es decir, palabras iguales pero con una terminación diferente (por ejemplo, si dice casa después no podría decir caserón, casucha, casita...). Qué otra palabra se le ocurre con la letra C?

1 minuto por cada letra.

P: piedra, plomo, pluma, paracaidas, papalote, cometa en mejicano

PD 20

Pe=12

piache, pañal, puñal, panza

PT=57

- Ahora le voy a decir otra letra y le voy a pedir, también, que diga todas las palabras que pueda que empiecen por esa letra lo más rápido posible. Recuerde que no valen nombres propios ni derivados de una misma palabra.

M: mamá, moises, marea, moño, miércoles, mierda, marihuana, miteando, mono, maiz, mina, misógeno, misántropo, monzón, milapie, manzilla, mineral, mito, massa

Pd 19

Pe=13

PT=60

- Ahora le voy a decir otra letra y le voy a pedir, de nuevo, que diga todas las palabras que pueda que empiecen por esa letra lo más rápido posible. Recuerde que no valen nombres propios ni derivados de una misma palabra.

R: ratón, rabia, ruso, ramadán (romania) "radolíes", razón, riesgo radiología, rosa, rimbombante, roña, reloj, ritmo, ruego, radillo, riñón

Pd 16

Pe=11

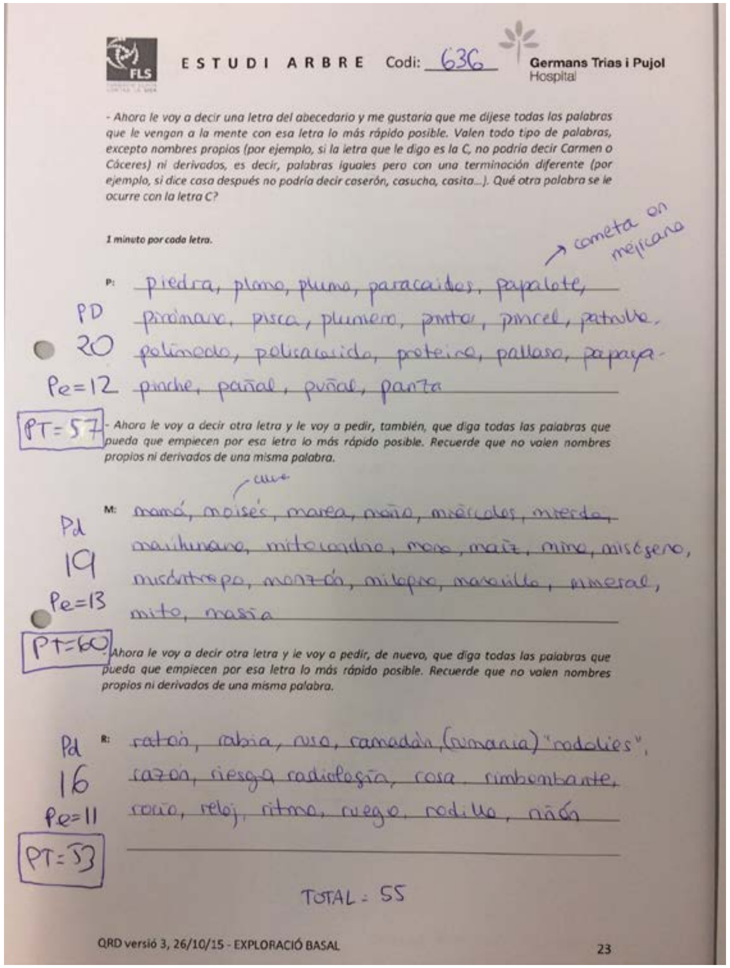
PT=53

TOTAL = 55

QRD versió 3, 26/10/15 - EXPLORACIÓ BASAL 23

- *Raw score:* ***19***
- *T score:* ***60***
- *Z score:* ***1.0***

Verbal Fluency
COWAT/PMR (Casals-Coll M, et al, 2013)



ESTUDI ARBRE Codi: 636 Germans Trias i Pujol Hospital

- Ahora le voy a decir una letra del abecedario y me gustaría que me dijese todas las palabras que le vengan a la mente con esa letra lo más rápido posible. Valen todo tipo de palabras, excepto nombres propios (por ejemplo, si la letra que le digo es la C, no podría decir Carmen o Cáceres) ni derivados, es decir, palabras iguales pero con una terminación diferente (por ejemplo, si dice casa después no podría decir caserón, casucha, casita...). Qué otra palabra se le ocurre con la letra C?

1 minuto por cada letra.

→ cometa en mexicano

P: piedra, plomo, pluma, paracaídas, papalote, primario, pisca, plumero, pinto, pincel, patrulla, polimeado?, policacuida?, proteína, payaso, papaya, pinche, pañal, puñal, panta

PD 20, Pe=12, PT=57

- Ahora le voy a decir otra letra y le voy a pedir, también, que diga todas las palabras que pueda que empiecen por esa letra lo más rápido posible. Recuerde que no valen nombres propios ni derivados de una misma palabra.

M: mamá, moisés, marea, maño, miércoles, mierda, marihuana, mitocondria, mono, maíz, mimo, misógeno, misántropo, manzana, milagro, mansilla?, mineral, mito, masa

Pd 19, Pe=13, PT=60

- Ahora le voy a decir otra letra y le voy a pedir, de nuevo, que diga todas las palabras que pueda que empiecen por esa letra lo más rápido posible. Recuerde que no valen nombres propios ni derivados de una misma palabra.

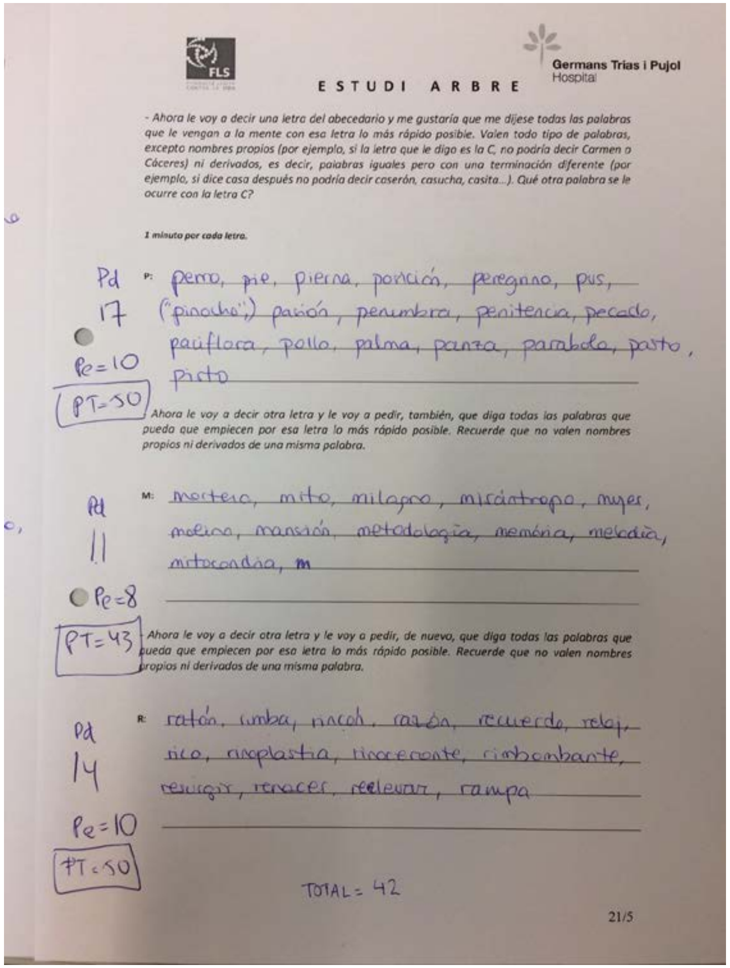
R: ratón, rabia, oso?, ramadán (romania) "rodolies", razón, riesgo, radiología, rosa, rimbombante, rocío, reloj, ritmo, ruego, rodillo, riñón

Pd 16, Pe=11, PT=53

TOTAL = 55

QRD versió 3, 26/10/15 - EXPLORACIÓ BASAL 23

- ➢ *Raw score:* ***19***
- ➢ *T score:* ***60***
- ➢ *Z score:* ***1.0***



ESTUDI ARBRE Germans Trias i Pujol Hospital

- Ahora le voy a decir una letra del abecedario y me gustaría que me dijese todas las palabras que le vengan a la mente con esa letra lo más rápido posible. Valen todo tipo de palabras, excepto nombres propios (por ejemplo, si la letra que le digo es la C, no podría decir Carmen o Cáceres) ni derivados, es decir, palabras iguales pero con una terminación diferente (por ejemplo, si dice casa después no podría decir caserón, casucha, casita...). Qué otra palabra se le ocurre con la letra C?

1 minuto por cada letra.

P: perro, pie, pierna, porción, peregrino, pus, ("pinocho") pasión, penumbra, penitencia, pecado, pasiflora, pollo, palma, panza, parábola, pasto, pisto

Pd 17, Pe=10, PT=50

- Ahora le voy a decir otra letra y le voy a pedir, también, que diga todas las palabras que pueda que empiecen por esa letra lo más rápido posible. Recuerde que no valen nombres propios ni derivados de una misma palabra.

M: mesero, mito, milagro, misántropo, mujer, molino, mansión, metodología, memoria, melodía, mitocondria, m

Pd 11, Pe=8, PT=43

- Ahora le voy a decir otra letra y le voy a pedir, de nuevo, que diga todas las palabras que pueda que empiecen por esa letra lo más rápido posible. Recuerde que no valen nombres propios ni derivados de una misma palabra.

R: ratón, rumba, rencor?, razón, recuerdo, reloj, rico, rinoplastia, rinoceronte, rimbombante, resurgir, renacer, relevar, rampa

Pd 14, Pe=10, PT=50

TOTAL = 42

21/5

- ➢ *Raw score:* ***8***
- ➢ *T score:* ***43***
- ➢ *Z score:* ***-0.7***

Right Answers

Information Processing Speed?

YES  **NO** 

Executive Functioning?

YES  **NO** 

Verbal Fluency?

YES  **NO** 

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Right Answers

Information

Executive F

Verbal Flue

***Source**: Clipartpanda.com*

Disclosure

Dr. Jose A. Muñoz-Moreno

May 2017

- Dr. Muñoz-Moreno has received **research funding** from AbbVie and ViiV Healthcare.
- Dr. Muñoz-Moreno has received **speaker honoraria** from Gilead Sciences, Merck Sharp & Dohme, and ViiV Healthcare.
- Dr. Muñoz-Moreno has received **consulting fees** from AlbaJuna Therapeutics, SL.

Learning Objectives

1. To summarize the recommendations made to measure cognition in HIV infection, and to point out the instruments and scores most commonly used.

2. To emphasize the relevance of the definition of change for HIV-related cognitive functioning, and to show the factors most importantly related to that definition.

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Outline

1. Measuring Cognition:

A. Non-HIV Populations: Recommendations

B. HIV Population: Recommendations

C. Measures of Change

2. Defining Change:

A. Setting & Design

B. Statistical Approach

C. Relevance of Time

D. Representative Examples

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Outline

1. Measuring Cognition:

A. Non-HIV Populations: Recommendations

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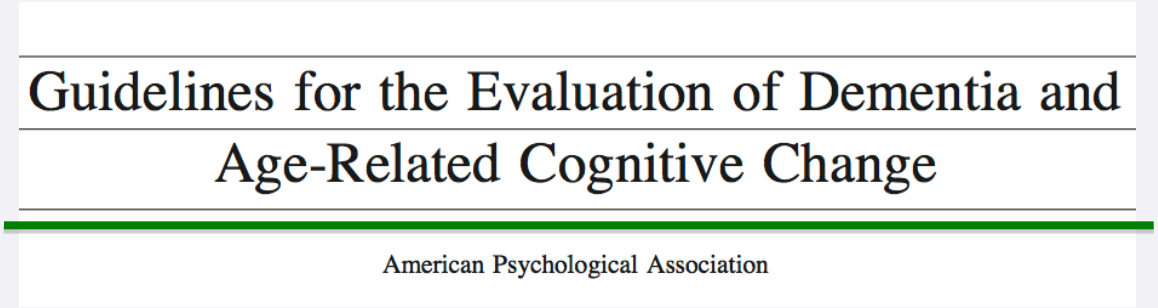
Measuring Cognitive Change in Non-HIV Populations



January 2012 • American Psychologist
© 2011 American Psychological Association 0003-066X/11/$12.00
Vol. 67, No. 1, 1–9 DOI: 10.1037/a0024643

- ***Neuropsychologists are uniquely equipped*** by training and expertise to assess changes in cognitive functioning and to distinguish ***normal changes from early signs of pathology***.

- ***Neuropsychological evaluation*** remains the ***most effective differential diagnostic method*** in discriminating dementia from age-related cognitive decline, symptoms that are depression related, and other related disorders.

- Despite of reliable ***biomarkers discovered***, cognitive testing will still be necessary ***to determine cognitive changes***, the rate of decline, the functional capacities of the individual, and hopefully, response to therapies.

Measuring Cognitive Change in Non-HIV Populations

ORIGINAL CONTRIBUTION

Mild Cognitive Impairments Predict Dementia in Nondemented Elderly Patients With Memory Loss

Andrea Bozoki, MD; Bruno Giordani, PhD; Judith L. Heidebrink, MD; Stanley Berent, PhD; Norman L. Foster, MD

Arch Neurol. 2001;58:411-416

Table 1. Neuropsychological Tests Used to Categorize Nondemented Subjects With Memory Impairment

Cognitive Function	Test*	Cut Score†
Language	Boston Naming Test	<47
Attention	WAIS-R Digit Span	<6
Visuospatial function	WAIS-R Block Design	<19
Frontal circuits	Controlled Oral Word Association Test	<18

**WAIS-R indicates Wechsler Adult Intelligence Scale–Revised.*
†Cut scores represent values 2 SDs below age-adjusted means.

Table 3. M+ Subjects With Abnormal Results on Each of the 4 Tests*

	No. (%)		
Subtest	Converters	Nonconverters	*P*
COWAT	5 (21)	1 (14)	.92
Boston Naming Test	10 (42)	1 (14)	.16
WAIS-R Block Design	15 (63)	4 (57)	.70
WAIS-R Digit Span	7 (29)	1 (14)	.50
≥2 Abnormal tests	11 (46)	0	.03

**M+ indicates impairment in 1 or more cognitive areas; COWAT, Controlled Oral Word Association Test; and WAIS-R, Wechsler Adult Intelligence Scale–Revised.*

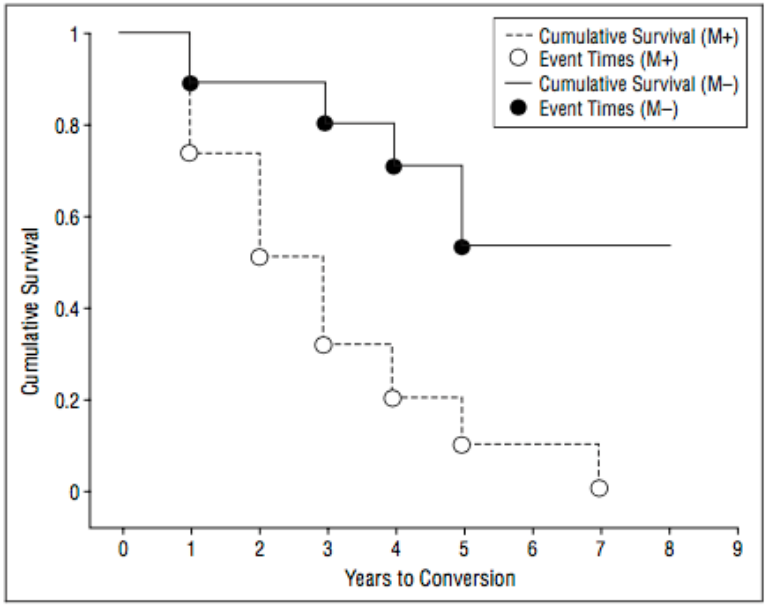


Figure 2. *Kaplan-Meier cumulative survival plot showing years to conversion to Alzheimer disease. M+ indicates impairment in 1 or more cognitive areas; M–, normal scores in all 4 cognitive areas apart from memory.*

Measuring Cognitive Change in Non-HIV Populations

Test
Speed and attention
Digit symbol
Trail making A
Trail making B
Digit span
Memory and learning
RAVLT delayed recall
Logical memory delayed recall
Rey complex figure delayed recall
Face recognition
Visuospatial function
VOSP silhouettes
Rey complex figure copy
Block design
Language
Token test
ASLD repetition
Boston naming test
Similarities
FAS word fluency
Executive function
PaSMO
Dual task my
WCST-CV64 correct
Stroop
Picture word test

PAPER

The Goteborg MCI study: mild cognitive impairment is a heterogeneous condition

A Nordlund, S Rolstad, P Hellström, M Sjögren, S Hansen, A Wallin

J Neurol Neurosurg Psychiatry 2005;**76**:1485–1490. doi: 10.1136/jnnp.2004.050385

Table 2 Proportion of subjects with results 1.5 SD below controls

Cognitive domain	Proportion of MCI 1.5 SD below controls
Speed and attention	40.2%
Learning and memory	48.2%
Visuospatial function	42.0%
Language	57.1%
Executive function	52.7%

MCI, mild cognitive impairment.

Table 3 Classification according to mild cognitive impairment (MCI) criteria

Subgroup	Proportion of MCI
No impairment	17.0%
I – amnestic	1.8%
II – multiple domains impaired	64.2%
III – single non-memory domain impaired	17.0%

Measuring Cognitive Change in Non-HIV Populations

Neuropsychological tests accurately predict incident Alzheimer disease after 5 and 10 years

Mary C. Tierney, PhD; Christie Yao; Alex Kiss, PhD; and Ian McDowell, PhD

NEUROLOGY 2005;64:1853–1859

Table 2 *Probability of Alzheimer disease (AD): results of logistic regression analyses and bootstrap validation of the relationship between diagnostic classification and variables in the predictive model for the 10-year and 5-year follow-up studies*

	Regression coefficient (p value)	Original OR (95% CI)	Bootstrap OR (95% CI)
10-Year follow-up study			
Intercept	−7.57 (0.006)		
Age, y	0.11 (0.003)	1.11 (1.04 to 1.19)	1.13 (1.06 to 1.23)
Education, y	−0.11 (0.04)	0.89 (0.80 to 0.99)	0.90 (0.77 to 1.03)
RAVLT Short Delay Recall	−0.18 (0.003)	0.84 (0.75 to 0.94)	0.78 (0.65 to 0.88)
5-Year follow-up study			
Intercept	−2.30 (0.24)		
Age, y	0.06 (0.02)	1.06 (1.01 to 1.11)	1.06 (1.01 to 1.11)
Education, y	0.07 (0.10)	1.07 (0.99 to 1.16)	1.07 (0.99 to 1.17)
RAVLT Short Delay Recall	−0.20 (<0.0001)	0.82 (0.74 to 0.90)	0.81 (0.72 to 0.90)
Animal Fluency	−0.15 (0.006)	0.86 (0.80 to 0.94)	0.86 (0.78 to 0.94)
WMS information	−0.35 (0.001)	0.71 (0.57 to 0.87)	0.70 (0.56 to 0.88)

For all three neuropsychological tests, the higher the score, the better the performance; thus a negative coefficient for these values indicates that the lower the score, the higher the probability of AD.

RAVLT = Rey Auditory Verbal Learning Test; WMS = Wechsler Memory Scale.

Outline

1. Measuring Cognition:

A. Non-HIV Populations: Recommendations

B. HIV Population: Recommendations

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Measuring Cognitive Change in HIV Population

Table. 1. Domains of the NIMH core neuropsychological battery

A. Indication of Premorbid Intelligence
   1. *Vocabulary (WAIS-R)*
   2. National Adult Reading Test (NART)

B. Attention
   1. Digit Span (WMS-R)
   2. *Visual Span* (WMS-R)

C. Speed of Processing
   1. Sternberg Search Task
   2. Simple and Choice Reaction Times
   3. *Paced Auditory Serial Addition Test* (PASAT)

D. Memory
   1. *California Verbal Learning Test* (CVLT)
   2. Working Memory Test
   3. Modified Visual Reproduction Test (WMS)

E. Abstraction
   1. Category Test
   2. Trails Making Test, Parts A and B

F. Language
   1. Boston Naming Test
   2. Letter and Category Fluency Test

G. Visuospatial
   1. Embedded Figures Test
   2. Money's Standardized Road-Map Test of Direction Sense
   3. Digit Symbol Substitution

H. Construction Abilities
   1. Block Design Test
   2. Tactual Performance Test

I. Motor Abilities
   1. Grooved Pegboard
   2. Finger Tapping Test
   3. Grip Strength

J. Psychiatric Assessment
   1. Diagnostic Interview Schedule (DIS)
   2. *Hamilton Depression Scale*
   3. *State-Trait Anxiety Scale*
   4. Mini-Mental State Examination

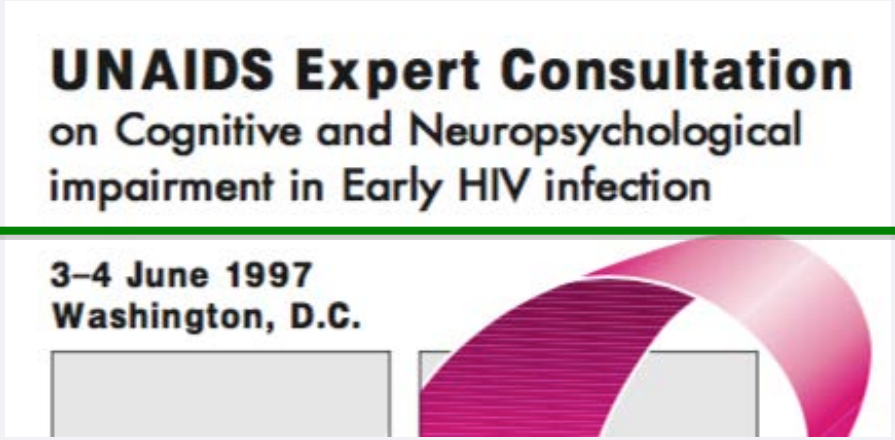
Italic indicates instruments in abbreviated version of the NIMH neuropsychological battery.

SPECIAL PRESENTATION

Assessment of Aids-Related Cognitive Changes: Recommendations of the NIMH Workshop on Neuropsychological Assessment Approaches*

Journal of Clinical and Experimental Neuropsychology
1990, Vol. 12, No. 6, pp. 963-978

Measuring Cognitive Change in HIV Population



UNAIDS
UNICEF • UNDP • UNFPA
UNESCO • WHO • WORLD BANK

- HIV has ***measurable consequences for performance on NP tests***. The majority of asymptomatic individuals, however, do not manifest ***significant impairment***.

- The diagnosis of HIV-related cognitive impairment based on NP tests has ***various limitations***, based on the comprehensiveness of the batteries, characteristics of the individuals, and settings where the tests are administered, ***including cultural contexts, and availability of appropriate normative standards***.

- The ***preferred method*** to assess cognitive changes is using ***NP tests over time***.

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Measuring Cognitive Change in HIV Population

Updated research nosology for HIV-associated neurocognitive disorders

Neurology 69 October 30, 2007

	Neuropsychological (NP) Testing is available
Asymptomatic Neurocognitive Impairment (ANI)	NP impairment in ≥ 2 cognitive domains that cannot be explained by opportunistic CNS disease, systemic illness, psychiatric illness, substance use disorders, or medications with CNS effects.
Mild Neurocognitive Disorder (MND)	At least mild NP impairment (>1 SD below a demographically appropriate normative mean), involving ≥2 cognitive domains.
HIV-Associated Dementia (HAD)	≥ Moderate NP impairment (>2SD below a demographically appropriate normative mean) on > 2 cognitive domains.

Fluency
- Controlled Oral Word Association Test (FAS) (1, 2)
- Thurstone Word Fluency Test (3)
- Category Fluency (4)
- Action Fluency (5)
- Design Fluency Tests (6, 7)

Executive Functions
- Stroop Color and Word Test (8)
- Trailmaking Test – Part B (3, 9)
- Color Trails –II (10)
- Wisconsin Card Sorting Test (11)
- Halstead Category Test (3, 9)
- Odd Man Out Test (12-14)
- Tower Tests (15-17)
- Delis-Kaplan Executive Function System (7)

Speed of Information Processing
- WAIS-III Digit Symbol Subtest (18)
- WAIS-III Symbol Search Subtest (18)
- Symbol Digit Modalities Test (19)
- Trailmaking Test – Part A (3, 9)
- Color Trails – I (10)
- Digit Vigilance Test (3, 20)
- Stroop Color Naming (8)
- Reaction Time Tests, e.g., California Computerized Assessment Battery (21)

Attention/Working Memory
- WAIS-III Digit Span Subtest (18)
- WAIS-III Letter-Number Sequencing Subtest (18)
- WMS-III Spatial Span Subtest (22)
- Paced Auditory Serial Addition Test (23)
- Digit Vigilance Test (error component) (3, 20)

Verbal and Visual Learning

Verbal:
- California Verbal Learning Test (Original and Revised; Total Learning) (24)
- Rey Auditory Verbal Learning Test (Total Learning) (25)
- Story Memory Test (Learning component) (3)

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Measuring Cognitive Change in Non-HIV Population

Neurocognitive Function in HIV-Infected Patients: Comparison of Two Methods to Define Impairment

Alejandro Arenas-Pinto[1,2*], Alan Winston[3,4], Wolfgang Stöhr[1], John Day[5], Rebecca Wiggins[6], Say Pheng Quah[7], Jonathan Ainsworth[8], Sue Fleck[1], David Dunn[1], Alex Accoroni[9] and Nicholas I. Paton[1,10] for the PIVOT Trial Team[¶]

July 2014 | Volume 9 | Issue 7 | e103498

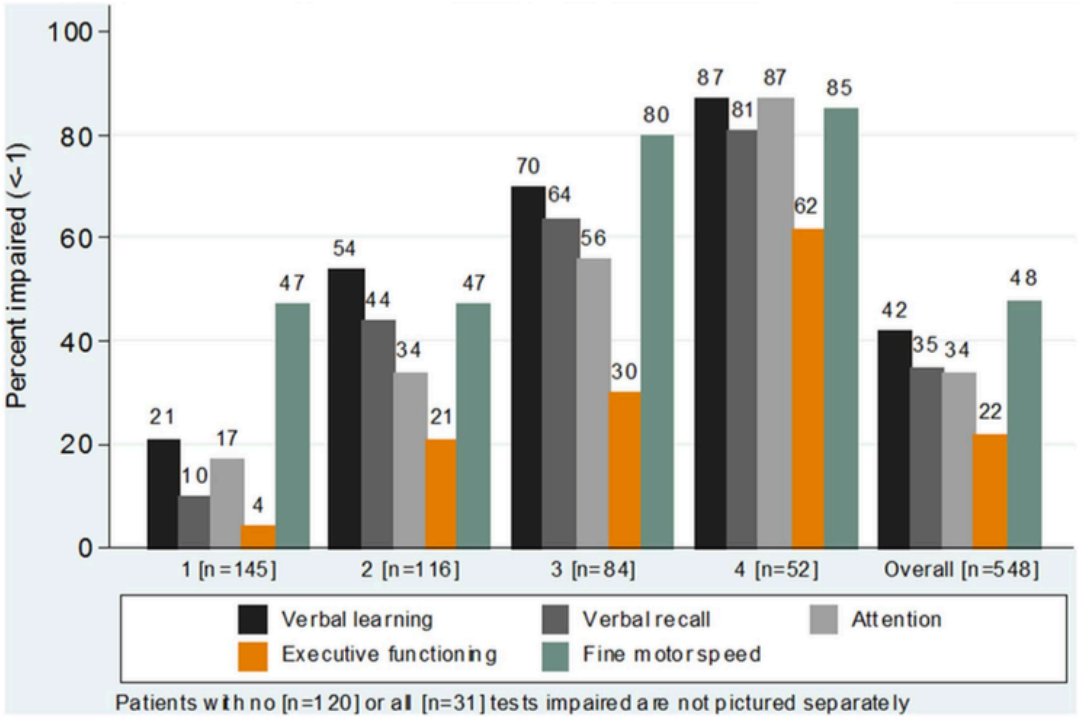

Figure 1. Proportion of patients with functional domains impaired (<−1SD), overall and by number of tests impaired.
doi:10.1371/journal.pone.0103498.g001

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Measuring Cognitive Change in HIV Population

Neurocognitive Function in HIV Infected Patients on Antiretroviral Therapy

Alan Winston[1,2*], Alejandro Arenas-Pinto[3,4], Wolfgang Stöhr[3], Martin Fisher[5], Chloe M. Orkin[6], Kazeem Aderogba[7], Andrew De Burgh-Thomas[8], Nigel O'Farrell[9], Charles J.N. Lacey[10], Clifford Leen[11,12], David Dunn[3], Nicholas I. Paton[3,13] for the PIVOT Trial Team[¶]

April 2013 | Volume 8 | Issue 4 | e61949

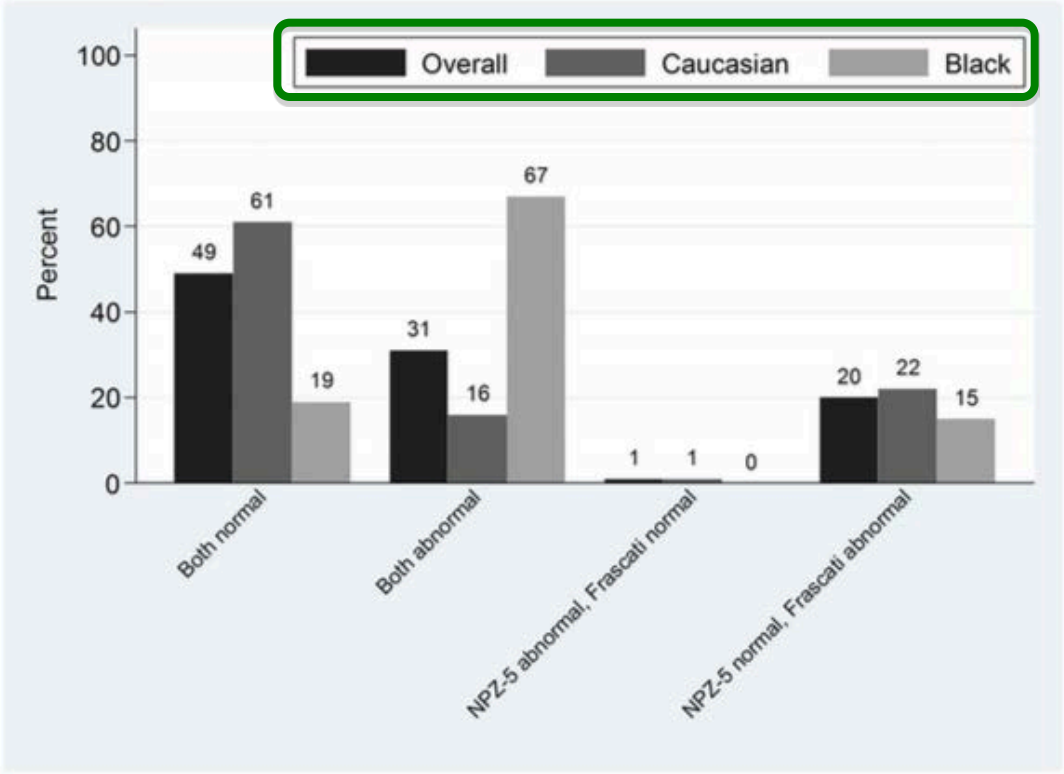

Figure 1. Association between NPZ-5 score and Frascati score.
doi:10.1371/journal.pone.0061949.g001

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Measuring Cognitive Change in Non-HIV Population

Assessment, Diagnosis, and Treatment of HIV-Associated Neurocognitive Disorder: A Consensus Report of the Mind Exchange Program

The Mind Exchange Working Group

HIV/AIDS • CID 2013:56 (1 April) • 1005

2. Comprehensive standard neuropsychological testing should be based on the following:

   a. A comprehensive test battery including at least 6 cognitive domains including verbal/language; attention/working memory; abstraction/executive function; memory functions (learning and recall); speed of information processing; and motor skills. CEBM 5; GOR D (Antinori et al., 2007)

   b. Standard computerised-based neuropsychological tests may be used by clinical neuropsychologists, or they may prefer paper and pencil version of the same tests. The importance is again in the use of standard and validated instruments for detection of HAND. See standard reference book Lezak et al., 2004

   c. Similar neuropsychological tests are recommended to be used for ANI, MND and HAD diagnosis, although a step-down battery is often more appropriate in patients with severe impairment. A standard assessment of independence in activities of daily living is needed to differentiate ANI, MND and HAD. CEBM 5; GOR D (Antinori et al., 2007; see also Al-Khindi et al., 2011; Cysique et al., 2010a; Muñoz-Moreno et al., 2008; Ellis et al., 2002; Heaton et al., 2010; Heaton et al., 2011; Robertson et al., 2007; Robertson et al. 2010; Vivithanaporn et al., 2010)

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Measuring Cognitive Change in Non-HIV Population

Assessment, Diagnosis, and Treatment of HIV-Associated Neurocognitive Disorder: A Consensus Report of the Mind Exchange Program

HIV/AIDS • CID 2013:56 (1 April) • 1005

The Mind Exchange Working Group

5. The use of normative data (to adjust for demographic/sociodemographic factors) is essential for the correct interpretation of standard neuropsychological tests with quantitative outcomes (See standard reference books: Heaton et al., 2004b; Lezak et al., 2004; Strauss et al, 2006). Note that the neuropsychologist will also use qualitative information (for example level of motivation, level of reading or writing proficiency, etc) to contextualise the quantitative results.

   a. In developing and developed countries the effects of age, education, and gender (as well as ethnicity in some countries) must be considered. See standard reference books Lezak et al., 2004; Strauss et al, 2006

   b. Geographic characteristics (such as coming from an urban versus rural environment) may need to be considered in addition to the traditional demographic factors in developing countries. See standard reference books Heaton et al., 2008; Lezak et al., 2004; Strauss et al, 2006

   c. Normative data should be selected to best represent the demographic references for a particular participant. In some instances, local norms based on a smaller sample size are recommended over non-local norms based on large sample sizes. See standard reference book Strauss et al, 2006

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Outline

1. Measuring Cognition:

A. Non-HIV Populations: Recommendations

B. HIV Population: Recommendations

C. Measures of Change

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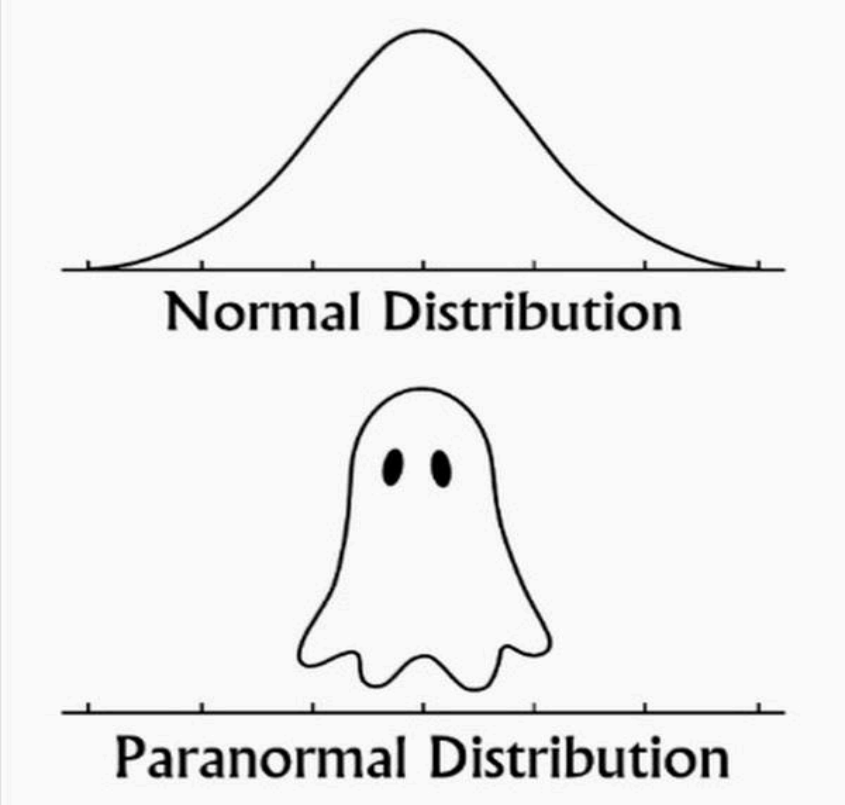
Type of Measures

- **Specific Cognitive Scores**
  vs
  Global Scores

  - ✓ *Multiple comparisons*
  - ✓ *Global representation*

- **RCI vs NPZ vs GDS:**

  - ✓ *Reliable Change Index*
  - ✓ *NeuroPsychological Z*
  - ✓ *Global Deficit Score*



***Source**: Alvinalexander.com*

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Cognitive Composite Scores

	Definition	*Formula*	*Recommendation*	*# Studies (longitudinal)*	*PROs*	*CONs*
RCI	Reliable Change Index	RCI = (Post - Pre) / S_{diff}* *$S_{diff} = \sqrt{2}(S_E)^2$	↑↑	5	1. Sensitivity / specificity 2. Integrative / change	1. Calculation
NPZ	Neuro Psychological Z Score	NPZ = ($z_1 + z_2 + ...$) / #z	↑	>30	1. Integrative 2. Calculation	1. No consensus selection
GDS	Global Deficit Score	GDS = *x* adapted T scores to deficit scores (0-5)	↓	7	1. Interpretation 2. Calculation	1. Limited range 2. Real benefits unconsidered

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C. Measures of Change

2. Defining Change:

A. Setting & Design

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Setting & Design Approach

1. Clinical vs Research:

- ☞ Number of measures considered
- ☞ Range of change

2. Research:

- ☞ Study design (prospective, randomized, controlled, ...)
- ☞ Endpoints established (primary vs secondary)
- ☞ Nº study arms
- ☞ Control group required
- ☞ Appropriate local normative data

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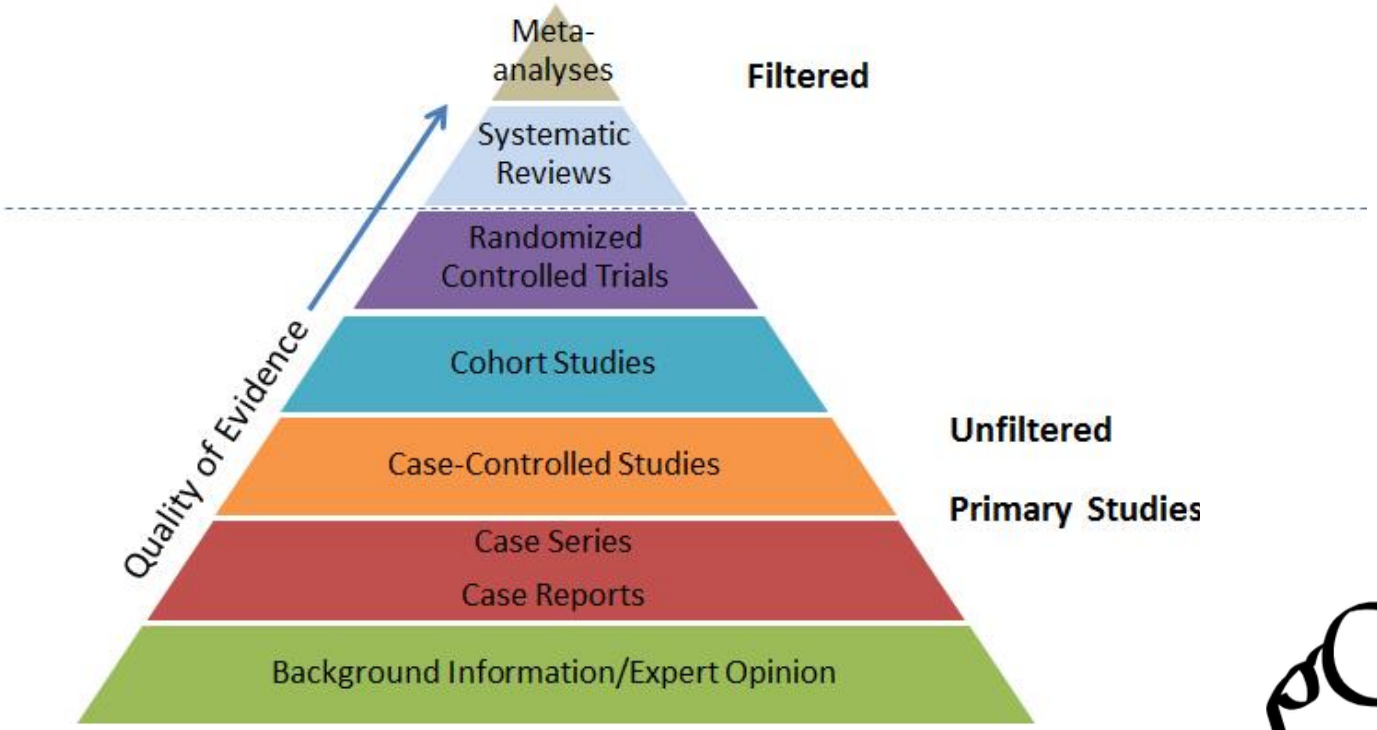
Setting & Design Approach



***Source**: Wakehealth.edu*

***Source**: Ourcommunitymedia.com*

Outline

1. Measuring Cognition:

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A. Setting & Design

B. Statistical Approach

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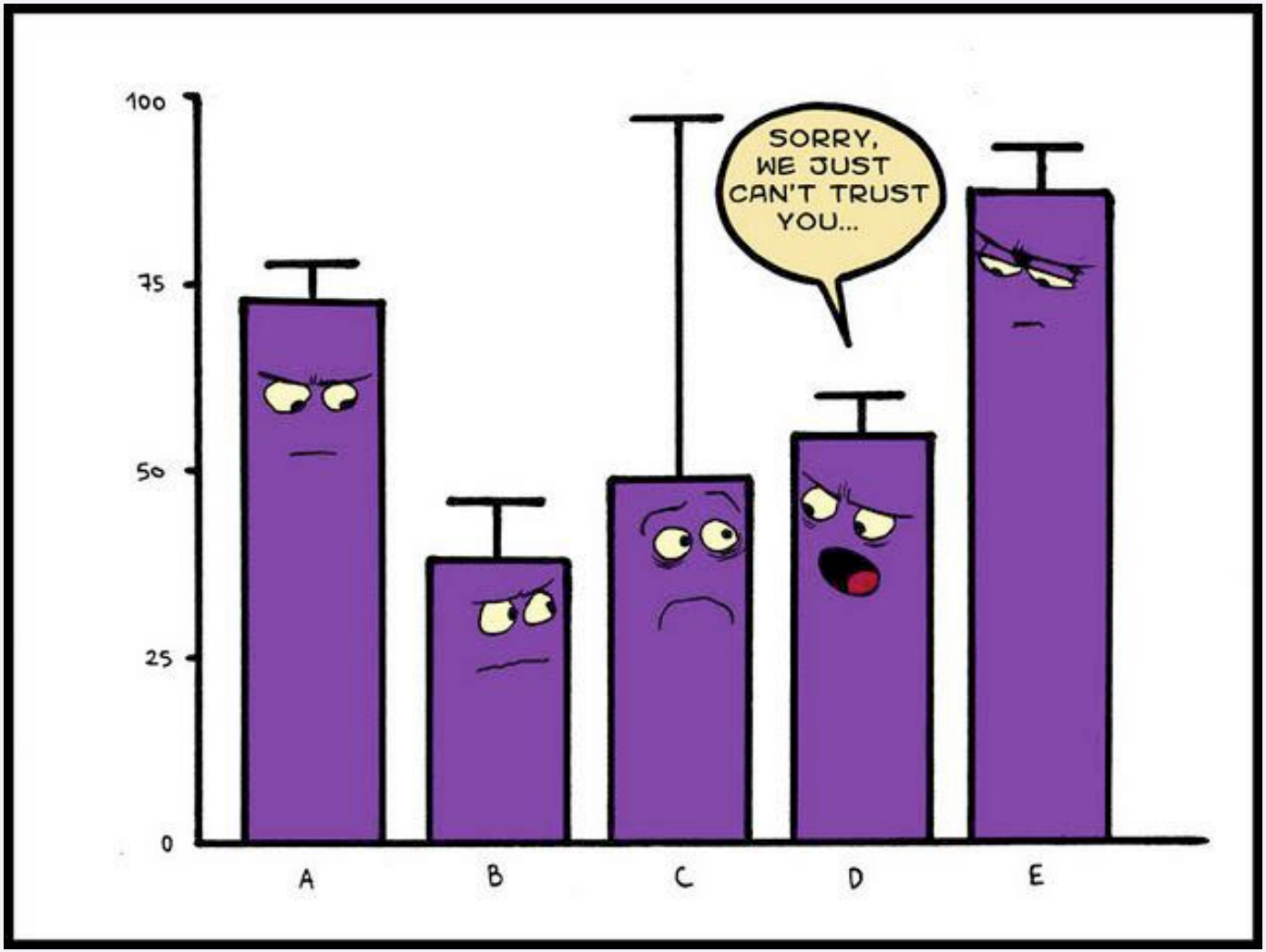
Relevance of Statistics



***Source**: Pinterest.com/jillthompsong*

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Relevance of Statistics

Tests

Characters	Parametric test	Non Parametric test
Testing mean, a hypothesized value	One sample t test	Sign test
Comparison of means of 2 groups	Independent t test	Mann Whitney U test
Means of related samples	Paired t test	Wilcoxon Signed rank test
Comparison of means of > 2 groups	ANOVA	Kruskal Wallis test
Comparison of means of > 2 related groups	Repeated measures of ANOVA	Friedman's test
Assessing the relationship between 2 quantitative variables	Pearson's correlation	Spearman's correlation

***Source**: Slideshare.net*

***Source**: finanz.com.mx*

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Relevance of Change Size, but also of Effect Size

☝ What is it really significant?

Effect Size	P value
• Substantive Significance • Does not depend upon sample size • Magnitude of difference between the two groups	• Statistically significance • Depends upon sample size and effect size • Examines whether finding is likely to be by chance. Inform reader if effect size exist or not, but not the size of the effect

***Source**: Linkedin.com*

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☝ What is it really significant?

PubMed.gov
US National Library of Medicine
National Institutes of Health

- cognitive change hiv (375) — PubMed
- cognitive change hiv significant (132) — PubMed
- cognitive change hiv effect size (7) — PubMed

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Relevance of Change Size, but also of Effect Size

☝ What is it really significant?

3. Impact of minocycline on cerebrospinal fluid markers of oxidative stress, neuronal injury, and inflammation in **HIV**-seropositive individuals with **cognitive** impairment.
Sacktor N, Miyahara S, Evans S, Schifitto G, Cohen B, Haughey N, Drewes JL, Graham D, Zink MC, Anderson C, Nath A, Pardo CA, McCarthy S, Hosey L, Clifford D; ACTG A5235 team..
J Neurovirol. 2014 Dec;20(6):620-6. doi: 10.1007/s13365-014-0292-0. Epub 2014 Nov 7.
PMID: 25377444 **Free PMC Article**
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4. Randomized trial of central nervous system-targeted antiretrovirals for **HIV**-associated neurocognitive disorder.
Ellis RJ, Letendre S, Vaida F, Haubrich R, Heaton RK, Sacktor N, Clifford DB, Best BM, May S, Umlauf A, Cherner M, Sanders C, Ballard C, Simpson DM, Jay C, McCutchan JA.
Clin Infect Dis. 2014 Apr;58(7):1015-22. doi: 10.1093/cid/cit921. Epub 2013 Dec 18.
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6. Randomized trial of minocycline in the treatment of **HIV**-associated **cognitive** impairment.
Nakasujja N, Miyahara S, Evans S, Lee A, Musisi S, Katabira E, Robertson K, Ronald A, Clifford DB, Sacktor N.
Neurology. 2013 Jan 8;80(2):196-202. doi: 10.1212/WNL.0b013e31827b9121. Epub 2012 Dec 26.
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B. Statistical Approach

C. Relevance of Time

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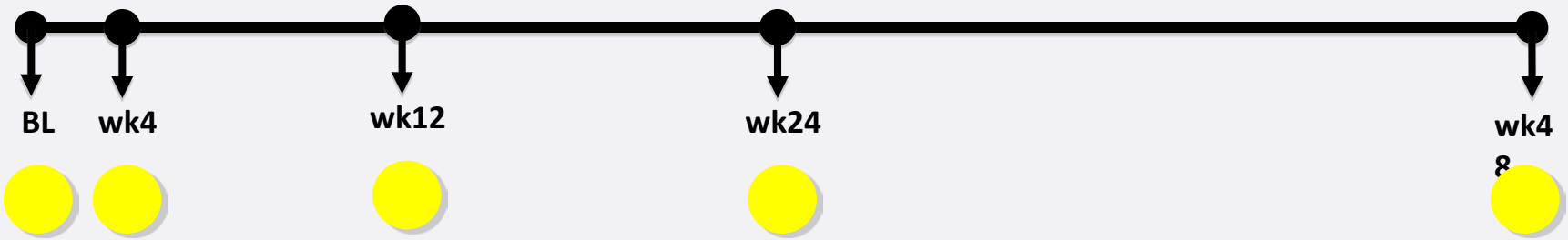
Relevance of Time



FUNDACIÓ LLUITA CONTRA LA SIDA

Practice Effect

Normative data and validation of a regression based summary score for assessing meaningful neuropsychological change

Lucette A. Cysique[1,2], Donald Franklin, Jr[1], Ian Abramson[1], Ronald J. Ellis[1], Scott Letendre[1], Ann Collier[3], David Clifford[4], Benjamin Gelman[5], Justin McArthur[6], Susan Morgello[7], David Simpson[7], J. Allen McCutchan[1], Igor Grant[1], Robert K. Heaton[1], the CHARTER group, and the HNRC group

JOURNAL OF CLINICAL AND EXPERIMENTAL NEUROPSYCHOLOGY
2011, 33 (5), 505–522

Category	*Test*
Verbal fluency	Animal fluency[a]
	Letter fluency[a]
Attention/working memory	PASAT-50[a]
	WAIS–III L–N Sequencing
Speed of information processing	WAIS–III Digit Symbol[a]
	WAIS–III Symbol Search
	Trail Making Test A
Executive functioning	WCST-64
	Trail Making Test B
Learning/memory	Verbal (Hopkins Verbal Learning Test–Revised) Total Learning & Delayed Recall
	Visual (Brief Visuospatial Memory Test–Revised) Total Learning & Delayed Recall
Motor	Grooved Pegboard dominant & nondominant hand[a]

TABLE 5
Median practice effect from baseline to follow-up on 15 NP measures

NP measure	*T2*	*T3*	*T4*	*T5 +*
Letter Fluency	0.0	0.5	1.0	1.0
Animal Fluency	0.0	0.0	0.0	0.0
PASAT-50	0.5	1.0	1.0	1.0
WAIS–III L–N Sequencing	0.0	0.0	0.0	0.0
WAIS–III Digit Symbol	0.0	0.5	1.0	1.0
WAIS–III Symbol Search	0.5	1.0	1.0	1.0
Trail Making Test A	0.5	1.0	1.0	1.0
WCST-64 Perseverative Errors	1.0	2.0	2.0	2.0
Trail Making Test B	1.0	1.0	1.0	1.0
HVLT–R Total Learning	0.0	1.0	0.5	0.5
HVLT–R Delayed Recall	0.5	0.5	0.5	0.5
BVMT–R Total Learning	1.0	1.0	0.0	1.0
BVMT–R Delayed Recall	0.5	0.0	0.0	0.5
Grooved Pegboard DH	0.5	0.0	1.0	1.0
Grooved Pegboard NDH	0.0	0.5	0.5	1.0
Sum	6.0	10.0	10.5	12.5

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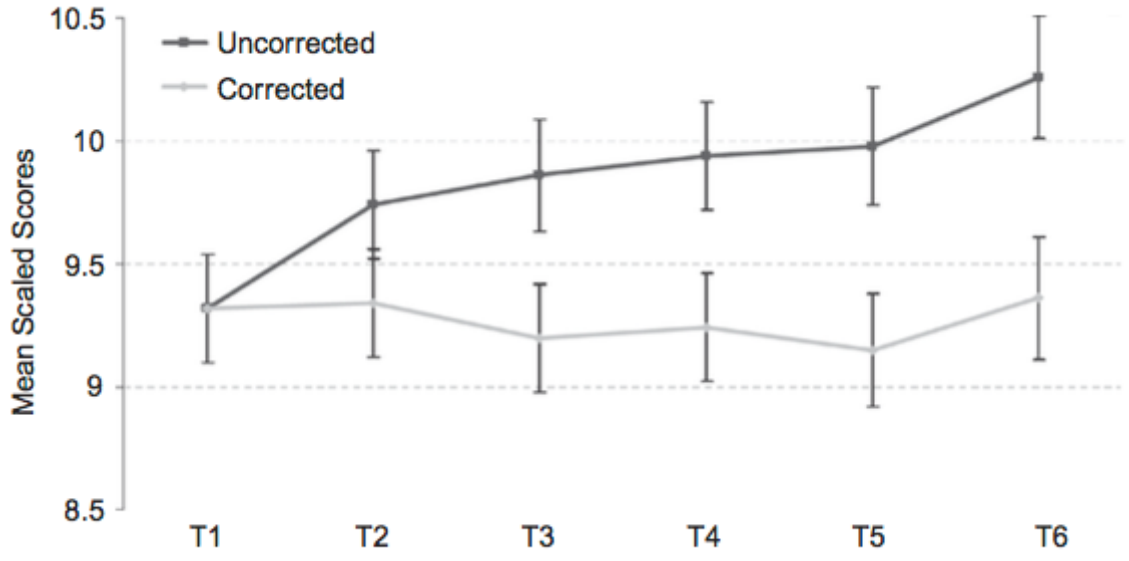

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B. Statistical Approach

C. Relevance of Time

D. Representative Examples

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Examples of Studies (1)

Lithium therapy for human immunodeficiency virus type 1–associated neurocognitive impairment

Giovanni Schifitto,[1,3] Jianhui Zhong,[2,3] David Gill,[4] Derick R Peterson,[5] Michelle D Gaugh,[1] Tong Zhu,[2] Madalina Tivarus,[3] Kim Cruttenden,[1] Sanjay B Maggirwar,[6] Howard E Gendelman,[7] Stephen Dewhurst,[8] and Harris A Gelbard[1,8]

Schifitto et al, J Neurovirol, 2009

Table 2 Neuropsychological and functional changes

	Baseline	Week 10	*P* value
Rey Auditory Verbal Memory (number correct)			
Total	32.47 (6.01)	37.14 (6.89)	.224
Trial 5	8.33 (2.26)	9.64 (2.17)	.089
Recall after Interference	6.33 (2.02)	5.93 (1.69)	.398
Delayed Recall	5.73 (2.25)	5.54 (1.81)	.556
Digit Symbol (number correct)	39.27 (9.50)	40.00 (8.99)	.760
Mean Reaction Time (ms)			
Choice	421.00 (38.20)	443.07 (48.81)	.033
Sequential	558.80 (150.77)	587.86 (162.80)	.357
Grooved Pegboard (s)			
Dominant Hand	77.07 (7.90)	73.57 (12.57)	.196
Non-dominant Hand	83.07 (12.02)	80.64 (13.99)	.504
Timed Gait (s)	8.64 (0.79)	8.05 (0.74)	.227
Neuropsychological z-score	0.62 (3.15)	2.32 (3.38)	.635
CES-D score	47.20 (10.95)	44.71 (12.05)	.486
FSS score	4.62 (1.63)	4.95 (1.62)	.596

Note. Values are mean (SD).

	Characteristics
Autor / Year	Schifitto et al / 2009
Design / Sample	Single-arm/ N = 15
Intervention	Lithium
Efficacy Endpoint	NPZ10 / 4 domains
Time	10 weeks
Statistical Approach	t test, p values
Results	No significant improvement

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Examples of Studies (2)

Minocycline treatment for HIV-associated cognitive impairment

Results from a randomized trial

Sacktor et al, Neurology, 2011

Table 3 Descriptive statistics for the 24-week change of individual NPZ scores and the NPZ-8[a]

	Treatment, mean (SD)				
	Placebo (n = 55)	Minocycline (n = 52)	Total (n = 107)	Minocycline effect, 95% confidence interval	*p* Value
Timed Gait change	0.08 (2.68)	0.22 (1.61)	0.15 (2.20)	−0.35, 1.36	0.244
Grooved Pegboard Dominant change	0.08 (0.75)	0.46 (1.19)	0.25 (0.99)	0.09, 0.92	0.017
Grooved Pegboard nondominant change	0.03 (0.77)	0.08 (0.76)	0.05 (0.76)	−0.18, 0.44	0.416
Trail Making A change	0.17 (1.12)	0.09 (0.84)	0.13 (1.00)	−0.47, 0.28	0.613
Trail Making B change	0.13 (0.97)	0.06 (0.83)	0.10 (0.91)	−0.40, 0.26	0.679
Symbol Digit change	−0.07 (0.92)	−0.15 (0.76)	−0.11 (0.85)	0.45, 0.28	0.637
Basic Choice Reaction Time change	0.23 (1.66)	0.04 (2.60)	0.14 (2.14)	−0.85, 0.54	0.663
Sequential Reaction Time change	0.18 (1.02)	0.24 (0.95)	0.21 (0.98)	−0.36, 0.39	0.938
NPZ-8 changes	0.17 (0.67)	0.12 (0.71)	0.15 (0.69)	−0.26, 039	0.651

Abbreviation: NPZ-8 = neuropsychological *z* score.
[a] Adjusted for baseline neuropsychological test score and highly active antiretroviral therapy CNS penetration score.

	Characteristics
Autor / Year	Sacktor et al / 2011
Design / Sample	Randomized, Double-Blind / N = 107
Intervention	Minocycline / Placebo
Efficacy Endpoint	NPZ8 / 3 domains
Time	24 weeks
Statistical Approach	t test, p values
Results	No significant improvement

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Examples of Studies (3)

Rivastigmine for HIV-associated neurocognitive disorders

A randomized crossover pilot study

Simioni et al, Neurology, 2013

	Mean combined outcome (SD)	F[b]	p Value
ADAS-Cog	−0.09 (1.14)	$F_{1,13} = 0.31$	0.589
RTI reaction time	−0.53 (2.94)	$F_{1,13} = 1.87$	0.195
RTI movement time	0.68 (2.62)	$F_{1,13} = 0.45$	0.512
RVIP	−0.12 (1.26)	$F_{1,13} = 0.03$	0.858
SWM errors	0.19 (1.24)	$F_{1,13} = 0.08$	0.786
SWM strategy	0.44 (0.88)	$F_{1,13} = 3.94$	0.068
Trail Making Test A	1.20 (1.89)	$F_{1,13} = 5.57$	0.034[c]
Trail Making Test B	0.22 (3.28)	$F_{1,13} = 0.06$	0.816
SOC correct problems	0.26 (0.95)	$F_{1,12} = 1.17$	0.301
Symbol Digit test	0.11 (0.66)	$F_{1,13} = 0.27$	0.613
Digit span backward	0.08 (2.17)	$F_{1,13} = 0.00$	0.946
Digit span forward	−0.03 (2.21)	$F_{1,13} = 0.03$	0.867
MOS-HIV perceived health[d]	0.20 (21.18)	$F_{1,13} = 0.06$	0.804
MOS-HIV social function[d]	−9.53 (56.09)	$F_{1,13} = 0.70$	0.418
MOS-HIV cognitive function[d]	16.87 (34.76)	$F_{1,13} = 2.71$	0.124
MOS-HIV mental health[d]	4.67 (31.24)	$F_{1,13} = 0.12$	0.730
MOS-HIV global quality of life[d]	14.73 (43.58)	$F_{1,13} = 1.45$	0.249

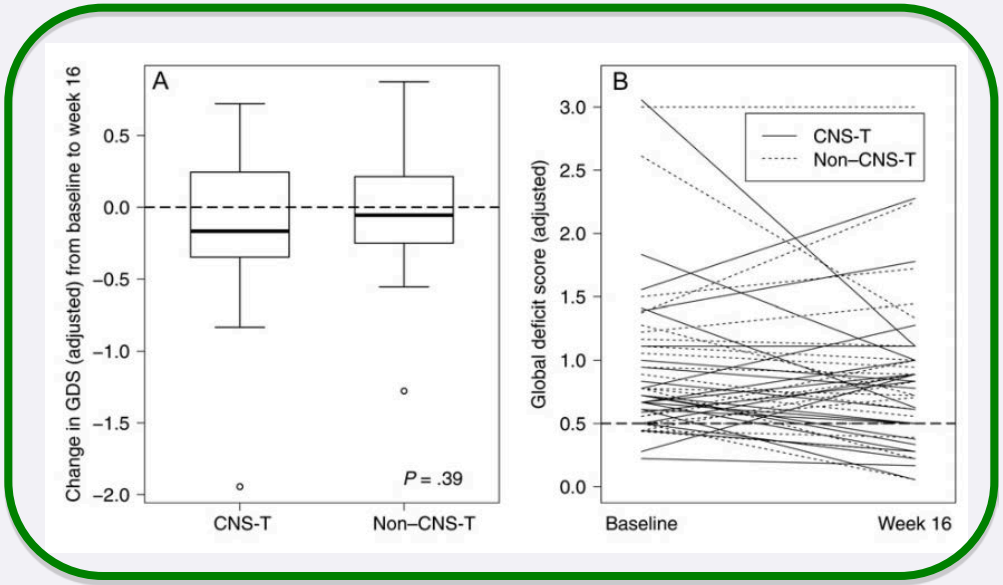
	Characteristics
Autor / Year	Simioni et al / 2013
Design / Sample	Cross-over, Pilot/ N = 17
Intervention	Rivastigmine
Efficacy Endpoint	Specific scores / 5 domains
Time	20 weeks
Statistical Approach	ANOVA, p values
Results	No significant improvement

Examples of Studies (4)

Randomized Trial of Central Nervous System–Targeted Antiretrovirals for HIV-Associated Neurocognitive Disorder

Ronald J. Ellis,[1] Scott Letendre,[2] Florin Vaida,[3] Richard Haubrich,[2] Robert K. Heaton,[4] Ned Sacktor,[7] David B. Clifford,[8] Brookie M. Best,[5] Susanne May,[9] Anya Umlauf,[4] Mariana Cherner,[4] Chelsea Sanders,[4] Craig Ballard,[6] David M. Simpson,[10] Cheryl Jay,[11] and J. Allen McCutchan[2]

Ellis et al, CID, 2014



	Characteristics
Autor / Year	Ellis et al / 2014
Design / Sample	Randomized, Controlled / N = 59
Intervention	cART: CNS-T vs Non-CNS-T
Efficacy Endpoint	GDS / 7 domains
Time	16 weeks
Statistical Approach	ANCOVA, p values, effect sizes
Results	No significant improvement

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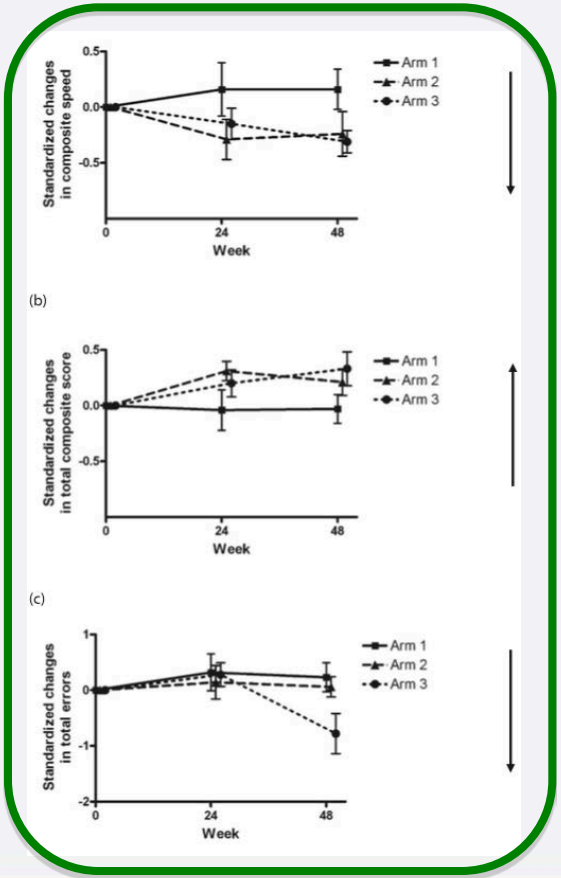
Examples of Studies (5)

Dynamics of cognitive change in HIV-infected individuals commencing three different initial antiretroviral regimens: a randomized, controlled study

A Winston,[1] R Puls,[2] SJ Kerr,[2,3] C Duncombe,[3] PCK Li,[4] JM Gill,[5] SD Taylor-Robinson,[1] S Emery[2] and DA Cooper[2] for the Altair Study Group

[1]Imperial College London, London, UK, [2]National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, NSW, Australia, [3]HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [4]Queen Elizabeth Hospital, Kowloon, Hong Kong and [5]Calgary Regional Health Authority, Calgary, Canada

Winston et al, HIV Medicine, 2012



	Characteristics
Autor / Year	Winston et al / 2012
Design / Sample	Randomized, Open-Label / N = 28
Intervention	cART: FTC + 1) EFV, 2) ATV/r, 3) AZT/ABC
Efficacy Endpoint	NPZ9 / 3 domains
Time	24 weeks + 48 weeks
Statistical Approach	t test, p values
Results	Significant improvements

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Examples of Studies (6)

RESEARCH ARTICLE

Differences in the Direction of Change of Cerebral Function Parameters Are Evident over Three Years in HIV-Infected Individuals Electively Commencing Initial cART

Alan Winston[1]*, Rebekah Puls[2], Stephen J. Kerr[2,3], Chris Duncombe[3], Patrick Li[4], John M. Gill[5], Reshmie Ramautarsing[3], Simon D. Taylor-Robinson[1], Sean Emery[2], David A. Cooper[2], for the ALTAIR Study Group[¶]

Winston et al, Plos ONE, 2015

Table 2. Changes in cerebral function parameters over 3 years.

Details		Mean absolute change				Mean absolute change		
		number	week 0–48	SD	*P-value*	week 48–144	SD	*P-value*
Cerebral Metabolite Ratio								
Anatomical area	Ratio							
Frontal Grey	*NAA/Cr*	22	0.31	0.66	0.36	0.13	0.91	1.00
	Cho/Cr	22	0.02	0.19	1.00	0.09	0.28	1.00
	ml/Cr	21	-0.27	1.35	1.00	1.13	1.71	0.06
Frontal White	*NAA/Cr*	22	0.04	0.74	1.00	0.14	0.77	1.00
	Cho/Cr	22	-0.08	0.30	1.00	0.14	0.24	0.09
	ml/Cr	21	-0.50	1.54	1.00	1.49	1.49	**0.002**
Right Basal Ganglia	*NAA/Cr*	20	0.64	1.20	0.27	-0.61	1.13	0.27
	Cho/Cr	20	-0.09	0.76	1.00	-0.17	0.33	0.27
	ml/Cr	20	-0.03	1.05	1.00	0.71	1.46	0.36
Cognitive test parameter								
Composite speed score	*decline in score represents improvement*	21	-0.186	0.486	0.10	-0.027	0.452	0.79
Composite accuracy score	*increase in score represents improvement*	21	0.220	0.497	0.06	-0.305	0.499	**0.01**
Executive function score	*decline in score represents improvement*	21	-0.222	0.858	0.25	0.351	1.20	0.19
Global composite score	*increase in score represents improvement*	21	0.627	1.16	**0.02**	-0.629	1.41	0.06

	Characteristics
Autor / Year	Winston et al / 2015
Design / Sample	Randomized, Open-Label / N = 22
Intervention	cART: FTC + 1) EFV, 2) ATV/r, 3) AZT/ABC
Efficacy Endpoint	NPZ9 / 3 domains
Time	48 weeks + 144 weeks
Statistical Approach	t test, p values
Results	Significant worsening

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Examples of Studies (7)

Transdermal Rivastigmine For HIV-Associated Cognitive Impairment: A Randomized Pilot Study

*Jose A. Muñoz-Moreno, MSc, PhD [1,2]; *Anna Prats, MSc [1,3]; José Moltó, MD, PhD [1]; Maite Garolera, MSc, PhD [4,5]; Núria Pérez-Álvarez, MSc, PhD [1,6]; Crisanto Díez-Quevedo, MD, PhD [3,7]; Cristina Miranda, RN [1]; Carmina R. Fumaz, MSc, PhD [1]; Maria J. Ferrer, MSc [1]; Bonaventura Clotet, MD, PhD [1,8,9]; and the TRIANT-TE Study Group*

Muñoz-Moreno et al, submitted, 2017

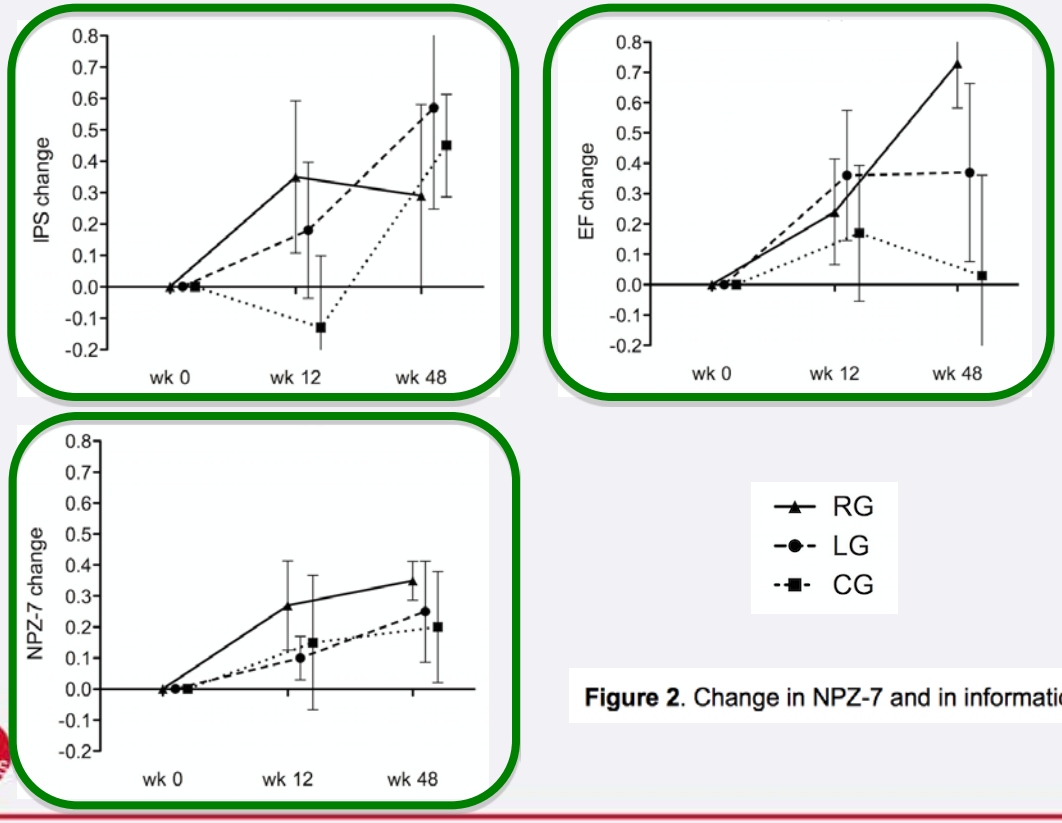

Figure 2. Change in NPZ-7 and in information processing speed and executive functioning domains.

	Characteristics
Autor / Year	Muñoz-Moreno et al / *submitted*
Design / Sample	Randomized, Controlled / N = 29
Intervention	Rivastigmine / Lithium / Control
Efficacy Endpoint	NPZ7 / 7 domains
Time	12 weeks + 48 weeks
Statistical Approach	ANOVA, p values, effect sizes
Results	No significant improvement

Conclusions

1. When assessing cognitive change, both the method and specific variables of change, and also the definition of change, are relevant aspects to consider.

2. Neuropsychological testing is the most widely recommended method to assess cognitive changes in HIV infection, and there are different scores that can be selected as measures of change.

3. Several aspects in the definition of change are crucial, in particular the study design, the timepoints, and mainly the statistical tests used.

4. The size of the change is a key point and must be analyzed adequately, preferably including effect sizes.

5. Only few of the multiple studies published in the field incorporate the same scores for change, and effect size tests.

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Thanks!

Jose A. Muñoz-Moreno, Ph.D.

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