Cognitive Impairment and Rehabilitation Following CNS Malaria in Ugandan Children

Michael Boivin, PhD, MPH[1,2]
Bruno Giordani, PhD[2]

1) Departments of Psychiatry and Neurology/Ophthalmology Michigan State University
2) Neuropsychology Division, Department of Psychiatry University of Michigan

Brain Disorders RO1 grants

R01HD064416 Boivin, Nakasujja (PIs) 04/01/2011-03/31/2016

Computerized Cognitive Rehabilitation in Children after Severe Malaria.

This study will evaluate the neuropsychological benefits of computerized cognitive rehabilitation therapy (CCRT) for Ugandan school children surviving severe malaria.

RO1NS055349 John (PI) 5/01/2008-4/30/2013

Pathogenesis of cognitive/neurologic deficits in central nervous system malaria (Uganda).

This study investigates the association of immunologic factors with neurocognitive sequelae in Ugandan children with severe malaria.

Other Funding Sources

R21 TW006794 John (PI) 9/1/2003-2/28/2007

Cognitive and neurologic sequelae of cerebral malaria

This study investigated the frequency of cognitive and neurologic sequelae and their association with immunologic factors, in children with cerebral malaria as compared to children with uncomplicated malaria and those without malaria.

University of Michigan Global Reach Faculty-Mentored Structured Summer Overseas Projects for Medical Students. Giordani, Boivin (PIs) 6/01/2010-8/31/2013

Cognitive rehabilitation with HIV positive children in Uganda.

Global Health Research and Training Award Giordani, Boivin (PIs) 1/01/2007-05/01/2008
University of Michigan Global Health Institute

The neuropsychological impact of a computerized cognitive rehabilitation training intervention with Ugandan cerebral malaria survivors.

Global Reach Faculty Development Award Giordani, Boivin (PIs) 6/01/2007-8/31/2008

University of Michigan Medical School

Neuropsychological, cognitive, and academic benefits of a computerized cognitive rehabilitation training intervention for HIV-infected Ugandan school children.

P. falciparum: CNS Malaria

- cerebral malaria
- severe malarial anemia
- acute renal insufficiency (“blackwater fever”)
- pulmonary edema/ ARDS
- metabolic acidosis
- hypoglycemia
- vascular collapse/ shock (“algid malaria”)

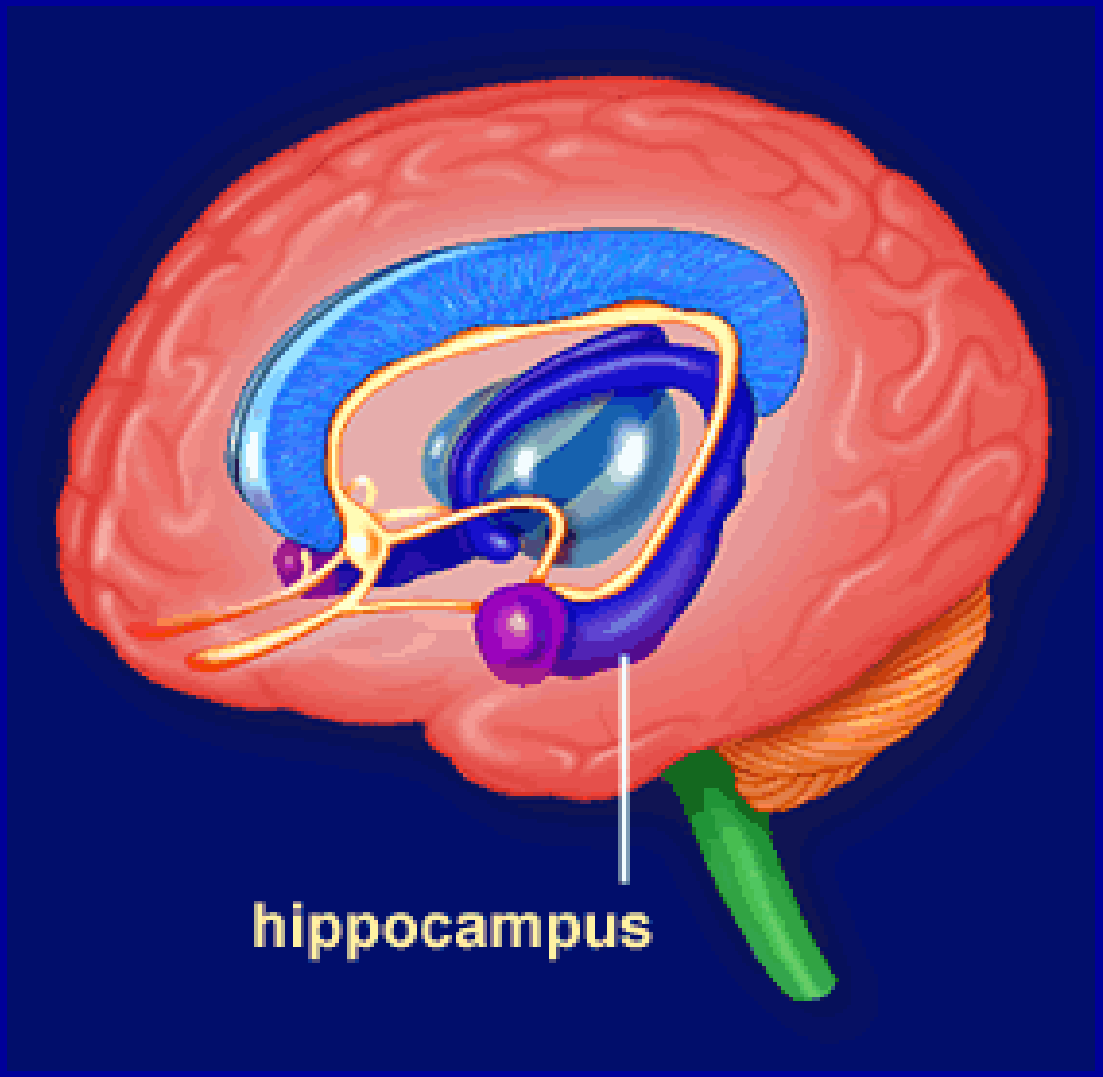
Child with Cerebral Malaria

Abnormal posturing, brain stem herniation, intracranial pressure.

Immunopathogenesis of Brain Injury in CM

- Do serum or CSF cytokine levels correlate with subsequent neurologic or cognitive impairment?

Areas of the Brain Mediating Visual-Spatial Mapping, Memory, and Learning



Kihara et al. (2010) *Journal of Neurological Sciences, 296,* 88-95

Areas of cognitive impairment in Cerebral Malaria – School Age

Author, Year	Areas of impairment
Muntendam, 1996	None
Dugbartey, 1998	Information processing
Holding, 1999*	Information processing, attention, language, behavior
Boivin, 2002	Attention, working memory
Carter, 2005*	Attention, memory, speech and language

Misdiagnosis of CM

- autopsy study of 31 children, 23% were misdiagnosed as having cerebral malaria

- **Retinopathy-** only clinical sign distinguishing malarial from nonmalarial coma. (Taylor et al., 2004)

- Malaria retinopathy-95% sensitivity, 90% specificity compared with autopsy findings (Birbeck et al., 2010).

Taylor et al., *Nat Med.* 2004 Feb;10(2):143-5. Epub 2004 Jan 25
Birbeck et al., *Am J Trop Med Hyg* 2010; 82: 231–34.

Figure 3: Typical CM retinopathy retinal hemorrhage with central whitening

Birbeck et al., *Am J Trop Med Hyg*, Feb 2010; 82: 231 - 234.

Study Objective

- Developmental assessments in children closer in age to the incident event (median 3.5 years) have not been carried out.

- Neurocognitive assessments in children with confirmed retinopathy-positive cerebral malaria have not been carried out.

Acknowledgements: This study would not have been possible without the excellent efforts of Maclean Vokhiwa, Theresa Nnensa, and Chimwemwe Kalengo

Malawi Developmental Assessment Tool

Melissa Gladstone (2010)

Gross Motor, Fine Motor, Language, Social Skills

Gladstone et al., *PLoS Medicine* 2010 7(5): e1000273

Tropical Medicine and International Health doi:10.1111/j.1365-3156.2010.02704.x

VOLUME ○○ NO ○○

Developmental outcomes in Malawian children with retinopathy-positive cerebral malaria

Michael J. Boivin[1], Melissa J. Gladstone[2], Maclean Vokhiwa[3], Gretchen L. Birbeck[1], Jed G. Magen[4], Connie Page[5], Margaret Semrud-Clikeman[4], Felix Kauye[6] and Terrie E. Taylor[7]

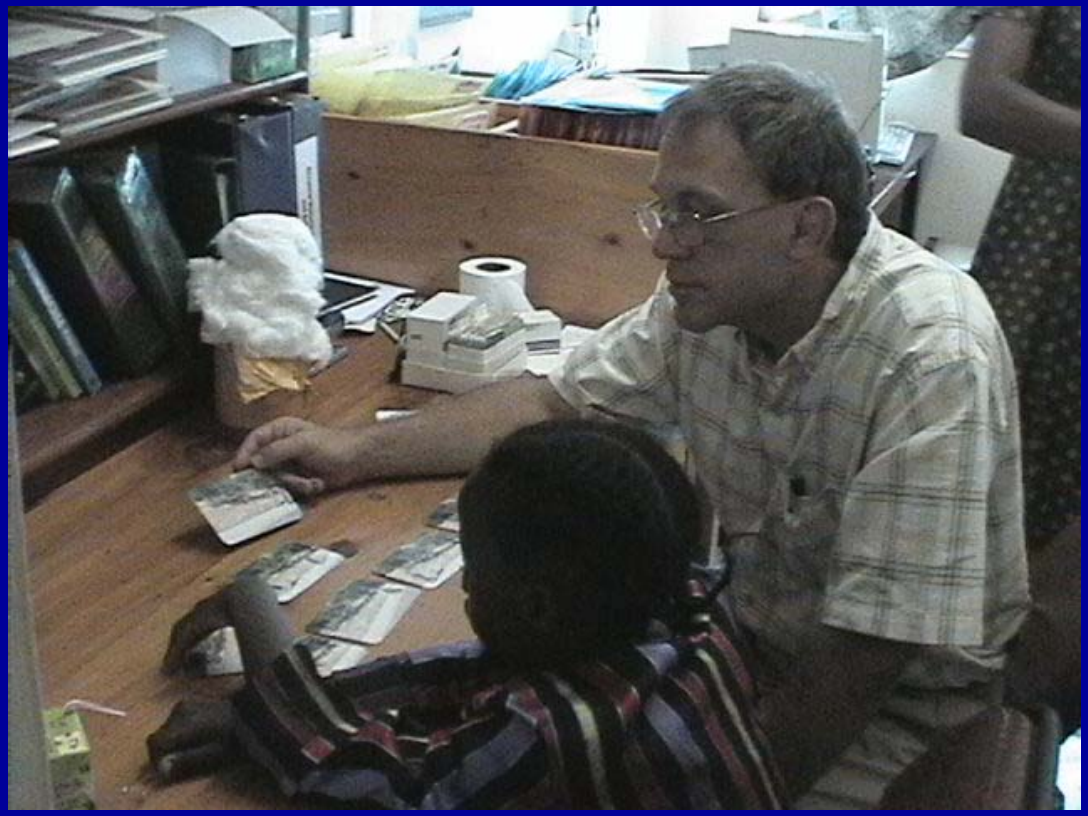
1 *International Neurologic and Psychiatric Epidemiology Program, Michigan State University, East Lansing, MI, USA*
2 *Institute of Child Health, University of Liverpool, Liverpool, UK*
3 *Blantyre Malaria Project, University of Malawi College of Medicine, Blantyre, Malawi*
4 *Department of Psychiatry, Michigan State University, ~~Place~~ East Lansing, MI, USA*
5 *Department of Statistics and Probability, Michigan State University, East Lansing, MI, USA*
6 *Office of the Chief of Psychiatry, Ministry of Health, Blantyre, Malawi*
7 *Department of Internal Medicine, College of Osteopathic Medicine, Michigan State University, East Lansing, MI, USA*

Pediatric Psychiatric Disorders Following Cerebral Malaria

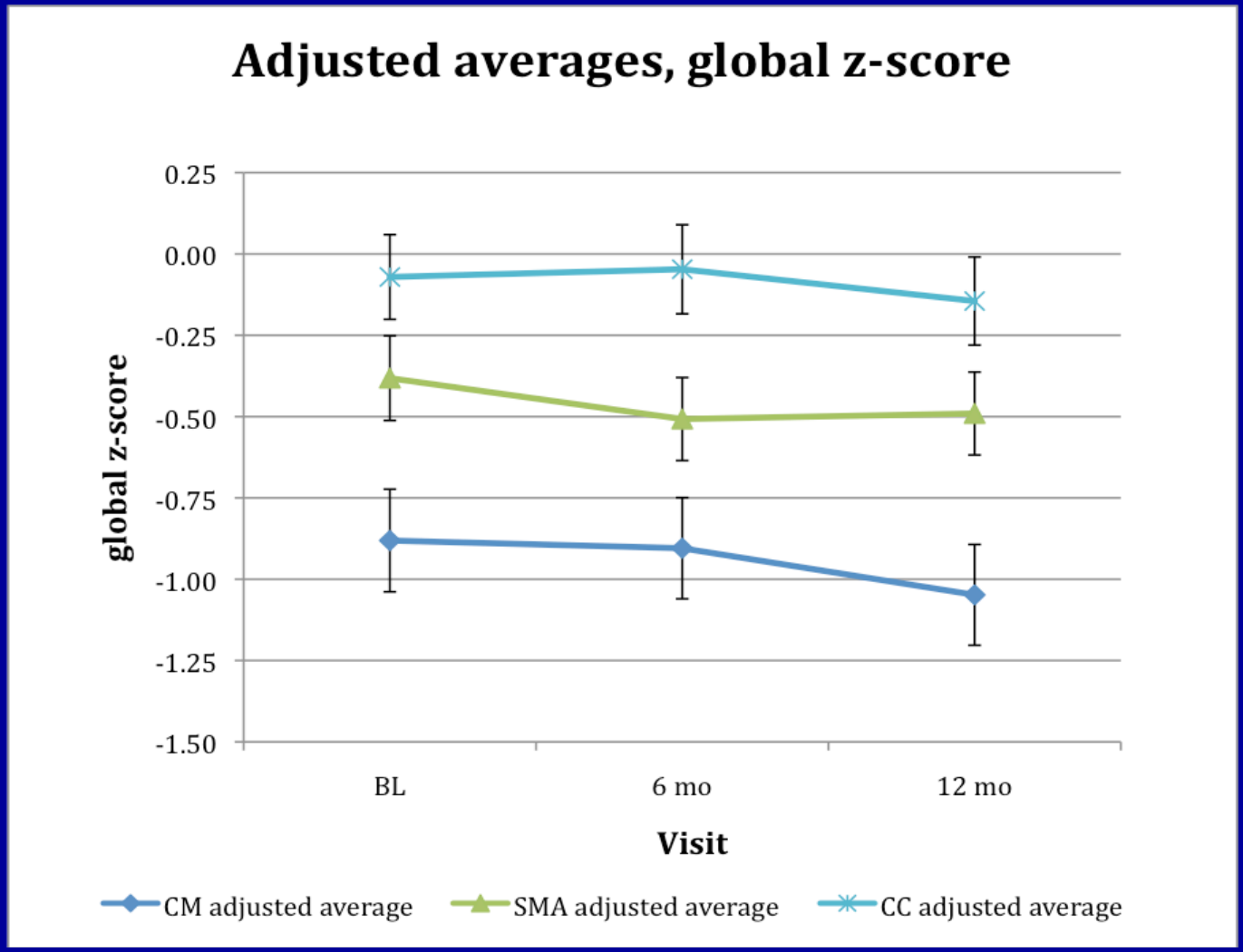
Evaluating the Achenbach Child Behavior Checklist (CBCL) as a Psychiatric Screening Tool for DSM IV Diagnoses in Malawian Children.

Conclusions. Children with a history of CM and behavior problems were most often diagnosed with ADHD and/or ODD. The CBCL had good predictive validity as a screening measure for ADHD. The "Rule Breaking" CBCL scale was sensitive to ODD.

Prospective study? Uganda Severe Malaria Research Program



Mullen Early Learning Scale Composite – Between Group



Mullen Early Learning Scale Composite – Between Group

Comparing groups at each visit

Effect	visit	Num DF	Den DF	F Value	P-value
GROUP*VISIT	0	2	360	7.54	0.0006
GROUP*VISIT	6	2	360	8.32	0.0003
GROUP*VISIT	12	2	360	9.90	<.0001

12-mo visit, comparing pairs of groups

group	group	Estimate	Standard Error	DF	P-value	95% Confidence Int Lower	Upper
1 minus	2	-0.5576	0.1880	360	0.0032	-0.9274	-0.1879
1 minus	3	-0.9033	0.2092	360	<.0001	-1.3147	-0.4919
2 minus	3	-0.3457	0.2058	360	0.0938	-0.7503	0.05895

Achenbach Child Development Checklist (CBCL) – Outcome Measures

- Internalizing Symptoms (depression, anxiety, withdrawal, somatic complaints)

- Externalizing Symptoms (aggressiveness, delinquent, psychosocial deviance)

Behavior Rating Inventory for Executive Function (BRIEF) (Caregiver administered)

- The Behavior Rating Inventory for Executive Function (BRIEF) evaluates behavioral and cognitive problems as they relate to disruption of executive functions of the brain from mild brain injury and/or developmental disorders. It is already translated into Luganda, Ateso, and Japhadola and will be translated into the local language(s) for Burkina Faso.
- The eight non-overlapping clinical scales form two broader indexes: **Behavior Regulation** (three scales) and **Metacognition** (five scales). A **Global Executive Composite** score is also produced.
- The scales include the behavior/cognitive functions of *Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor*.

Cerebral Malaria

Do children who recover from cerebral malaria have cognitive and/or psychiatric disability following discharge, 6-month follow-up, 1 year follow-up, and 2 years follow-up?

Best Practices in Developmental and Neuropsychological Assessment

- Predictive validity of assessment battery by age group/tests
- Sensitivity and specificity of assessment battery for clinical groups and interventions
- Cultural adaptation and translation
- Controlling for factors that affect developmental and neuropsychological outcomes (methodological and statistical)
- Proprietary considerations and cost for scaling cognitive interventions and assessments

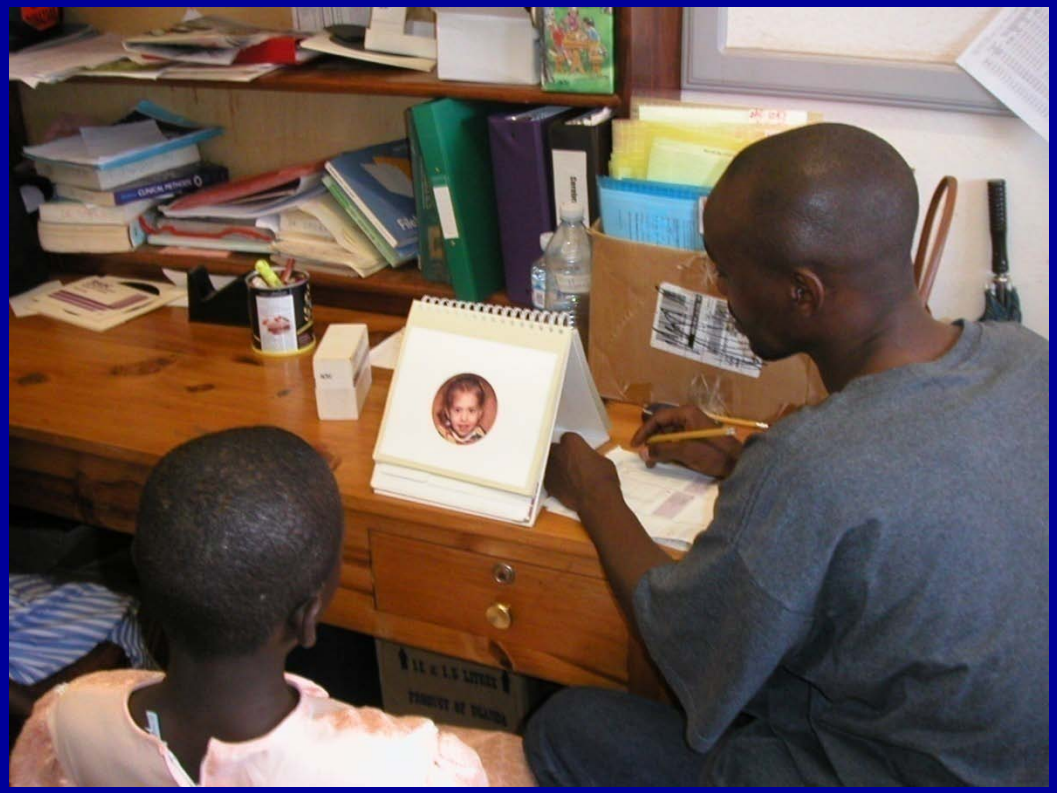
Regression coefficients showing the association between similar abilities in the different age groups

Measures	Mullen Visual reception	ECVT Vigilance	Early learning composite
KABC Simultaneous processing	0.06 (0.03 to 0.08), <0.001		
KABC Learning			0.01 (0.01 to 0.02), <0.001
KABC Planning	0.04 (0.0005 to 0.08), 0.05		
KABC Knowledge			0.01 (0.003 to 0.01), <0.002
TOVA Attention		2.78 (1.41 to 4.16), <0.001	
KABC Fluid crystallised index			1.29 (0.94 to 1.64), <0.001

Comparing HIV+ and HIV- Groups on KABC-2 (Ruel et al., 2012)

- Memory (***P* =.005**)
- Visual-spatial (***P* =.039**)
- Learning (***P* = .106**)
- Reasoning (*P* = .23)

*ANCOVA test with age, gender, SES, HOME as covariates.



A preliminary examination of the construct validity of the KABC-II in Ugandan children with a history of cerebral malaria

[a,b]Bangirana P*, [a]Seggane-Musisi, [b]Allebeck P, [c]Giordani B, [d]John CC, [e]Opoka OR, [e]Byarugaba J, [f,g]Ehnvall A, [c,h]Boivin MJ

a Department of Psychiatry, Makerere University School of Medicine, Kampala, Uganda
[b] Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden
[c] Neuropsychology Section, Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA
[d] Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA
[e] Department of Pediatrics and Child Health, Makerere University School of Medicine, Kampala, Uganda
[f] Institute of Clinical Neurosciences, Department of Psychiatry, Gothenburg University, Gothenburg, Sweden
[g] Center for Cognitive Therapy, Gothenburg, Sweden
[h] International Neurologic and Psychiatric Epidemiology Program, Michigan State University, East Lansing, MI, USA

Abstract

Background: Several diseases and adverse conditions affect the cognitive development of children in Sub-Saharan African. There is need to assess these children to determine which abilities are affected and the severity of the damage so as to plan interventions accordingly. However most psychological tests developed in the West have not been validated in this region making it impossible to know whether they measure what they were intended to in African children.

Objective: To examine the construct validity of the Kaufman Assessment Battery for Children, Second Edition (KABC-II) in Ugandan children.

Methods: Sixty five Ugandan children aged 7 to 16 years (Mean=9.90, SD=2.46) were tested using the KABC-II 44.59 months (SD=2.82) after an episode of cerebral malaria. The KABC-II scales of Sequential Processing, Simultaneous Processing, Planning and Learning were administered. In order to identify which factors result from administering the KABC-II in these children, factor analysis using principal component analysis with Varimax rotation was applied to the subtests making up the above scales.

Results: Five factors emerged after factor analysis comprising of subtests measuring Sequential Processing, Simultaneous Processing, Planning and Learning. The fifth scale comprised of subtests measuring immediate and delayed recall.

Conclusion: This preliminary study in Ugandan children shows the KABC-II to have good construct validity with subtests measuring similar abilities loading on the same factor. The KABC-II can be used in assessing Ugandan children after a few modifications. Further analysis of its psychometric properties in Ugandan children is required.

Key Words: neuropsychology, cross-cultural, Africa, children, validation

African Health Sciences 2009; 9(3): 186-192

OPEN ACCESS Freely available online

PLoS one

Socioeconomic Predictors of Cognition in Ugandan Children: Implications for Community Interventions

Paul Bangirana[1,2]*, Chandy C. John[3], Richard Idro[4], Robert O. Opoka[4], Justus Byarugaba[4], Anne M. Jurek[3], Michael J. Boivin[5,6]

1 Department of Psychiatry, Makerere University School of Medicine, Kampala, Uganda, 2 Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden, 3 Department of Pediatrics, University of Minnesota Medical School, Minneapolis, Minnesota, United States of America, 4 Department of Paediatrics and Child Health, Mulago Hospital/Makerere University School of Medicine, Kampala, Uganda, 5 International Neurologic and Psychiatric Epidemiology Program (INPEP), Michigan State University, East Lansing, Michigan, United States of America, 6 Neuropsychology Section, Department of Psychiatry, University of Michigan, Ann Arbor, Michigan, United States of America

Abstract

Background: Several interventions to improve cognition in at risk children have been suggested. Identification of key variables predicting cognition is necessary to guide these interventions. This study was conducted to identify these variables in Ugandan children and guide such interventions.

Methods: A cohort of 89 healthy children (45 females) aged 5 to 12 years old were followed over 24 months and had cognitive tests measuring visual spatial processing, memory, attention and spatial learning administered at baseline, 6 months and 24 months. Nutritional status, child's educational level, maternal education, socioeconomic status and quality of the home environment were also measured at baseline. A multivariate, longitudinal model was then used to identify predictors of cognition over the 24 months.

Results: A higher child's education level was associated with better memory ($p = 0.03$), attention ($p = 0.005$) and spatial learning scores over the 24 months ($p = 0.05$); higher nutrition scores predicted better visual spatial processing ($p = 0.002$) and spatial learning scores ($p = 0.008$); and a higher home environment score predicted a better memory score ($p = 0.03$).

Conclusion: Cognition in Ugandan children is predicted by child's education, nutritional status and the home environment. Community interventions to improve cognition may be effective if they target multiple socioeconomic variables.

Citation: Bangirana P, John CC, Idro R, Opoka RO, Byarugaba J, et al. (2009) Socioeconomic Predictors of Cognition in Ugandan Children: Implications for Community Interventions. PLoS ONE 4(11): e7966. doi:10.1371/journal.pone.0007966

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*E-mail: pbangirana@yahoo.com

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BioMed Central

Research

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Reliability of the Luganda version of the Child Behaviour Checklist in measuring behavioural problems after cerebral malaria

Paul Bangirana*[1,2], Noeline Nakasujja[1,2], Bruno Giordani[3], Robert O Opoka[4], Chandy C John[5] and Michael J Boivin[3,6]

Address: [1]Department of Psychiatry, Makerere University School of Medicine, Kampala, Uganda, [2]Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden, [3]Neuropsychology Section, Department of Psychiatry, University of Michigan, Ann Arbor, Michigan, USA, [4]Department of Pediatrics and Child Health, Makerere University School of Medicine, Kampala, Uganda, [5]Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota, USA and [6]International Neurologic and Psychiatric Epidemiology Program, Michigan State University, East Lansing, Michigan, USA

Email: Paul Bangirana* - pbangirana@yahoo.com; Noeline Nakasujja - drnoeline@yahoo.com; Bruno Giordani - giordani@med.umich.edu; Robert O Opoka - opokabob@yahoo.com; Chandy C John - ccj@umn.edu; Michael J Boivin - michael.boivin@hc.msu.edu

* Corresponding author

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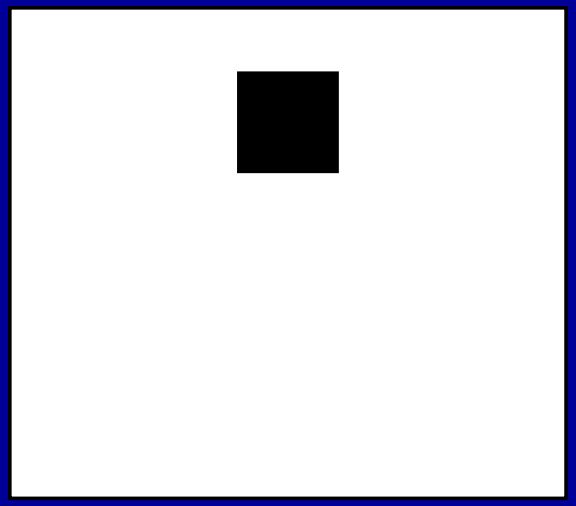
Test of Variables of Attention (TOVA): Visual and Auditory

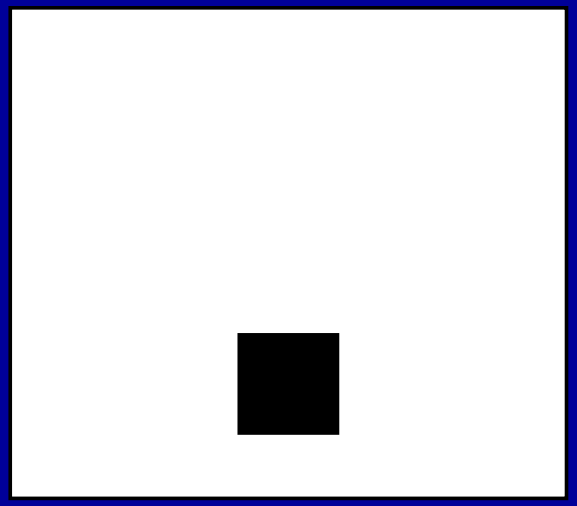
Test of Variables of Attention (TOVA)

Visual

Target



Non Target



Comparing HIV+ and HIV- Groups on TOVA-visual

D prime signal detection (*P* = .87)

Omission Errors (*P* = .37)

Commission Errors (*P* = .35)

Response Time **(*P* = .005)**

Response Time Var. (*P* = .24)

ADHD Score **(*P* = .03)**

*ANCOVA test on linear Studentized Residual Errors to age. SES and Gender as covariates

Test of Variables of Attention (TOVA) Auditory Test

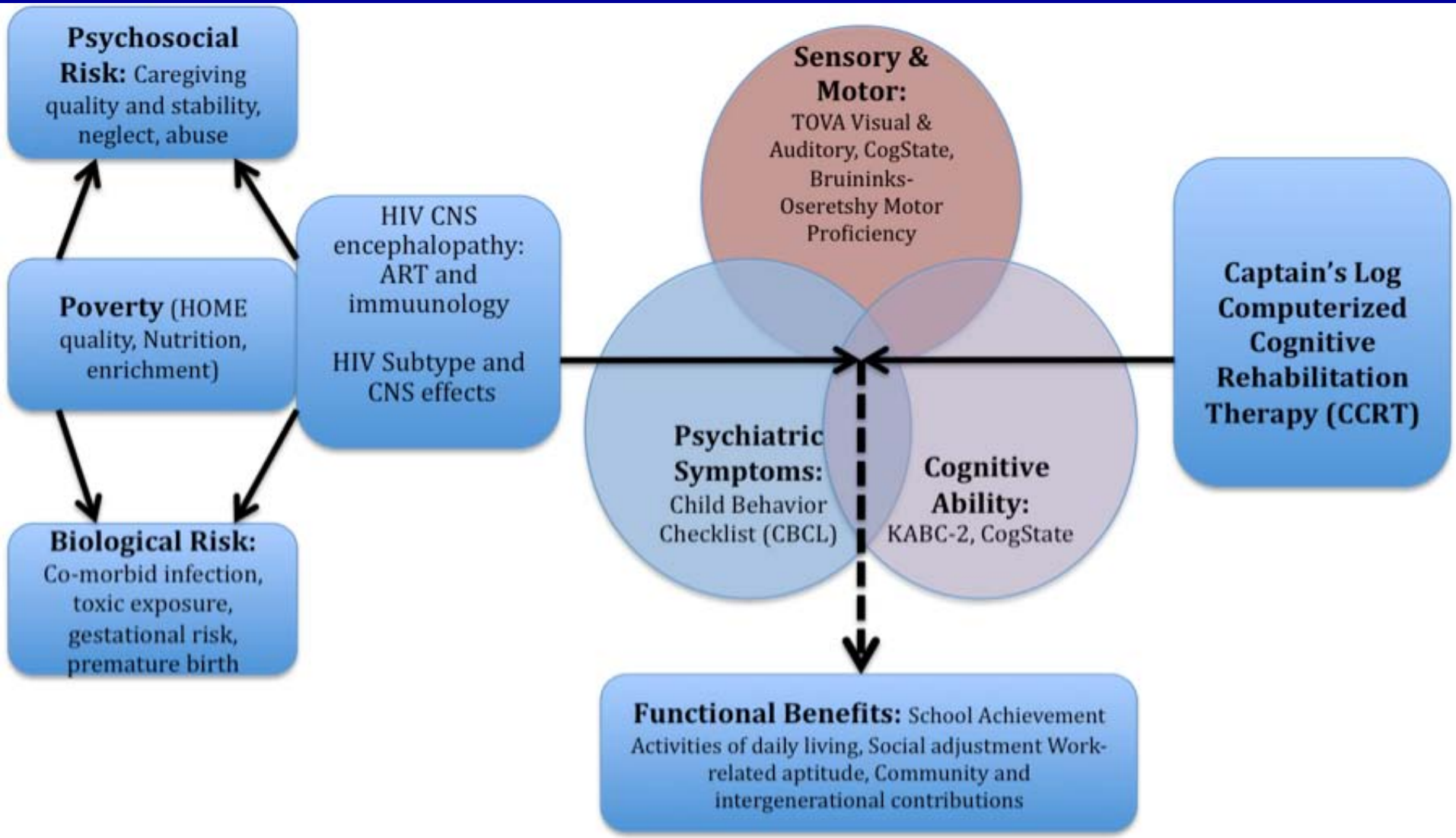
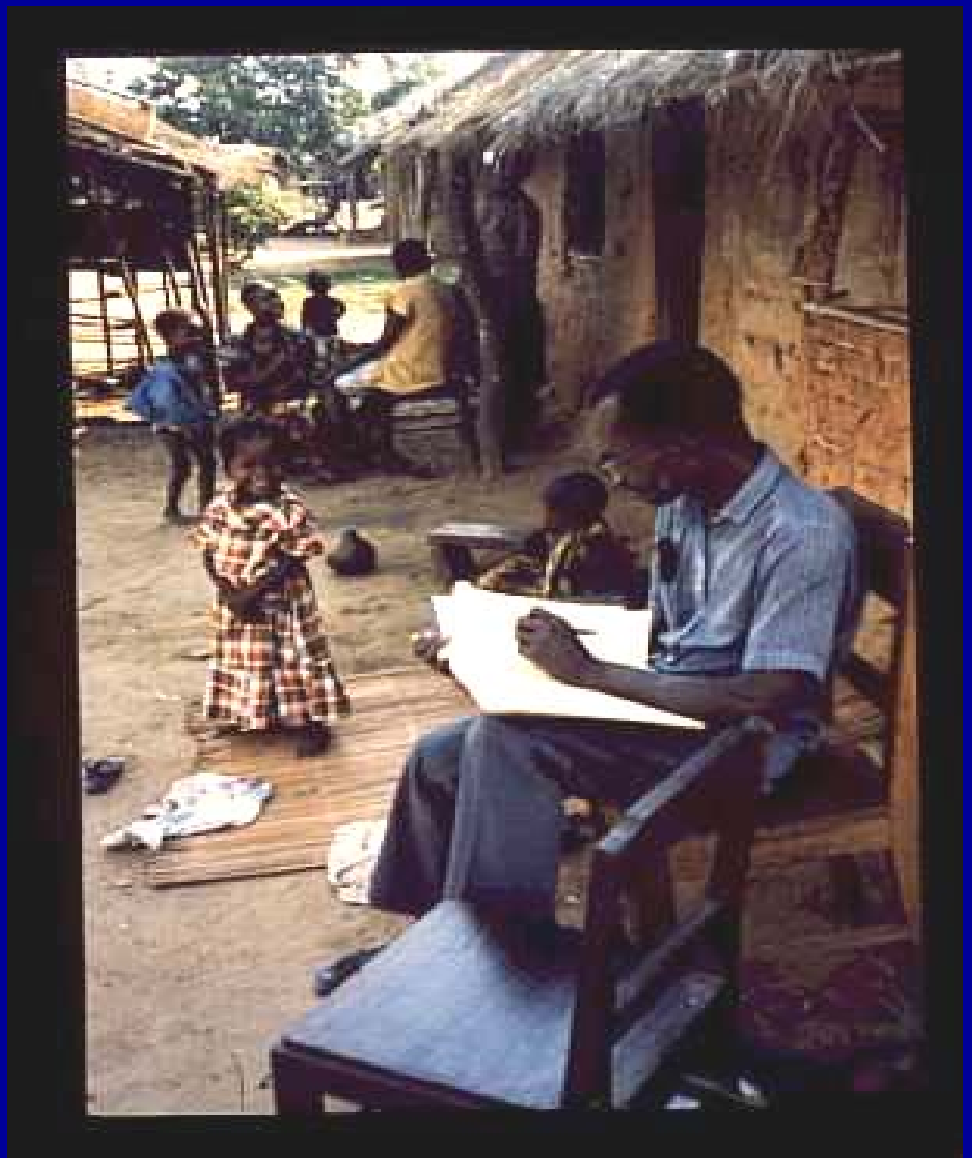


Figure 1: Model of the major risk factors and developmental domains for our study children with HIV. Adapted from Walker et al., 2007 & Engle et al., 2007.

Controlling for Quality of Home Environment (Uganda modified Caldwell MC-HOME; SES Quality of Physical Environment, or MICS4 Child Development)



Quality of caregiving in feeding, bathing, and shared-work interactions.

Emotional Wellbeing of Caregivers (e.g., Depression; Hopkins Symptoms Checklist – 25 items)

Effects of Malnutrition, Stunting, Developmental Delay on Neuropsychological Outcomes

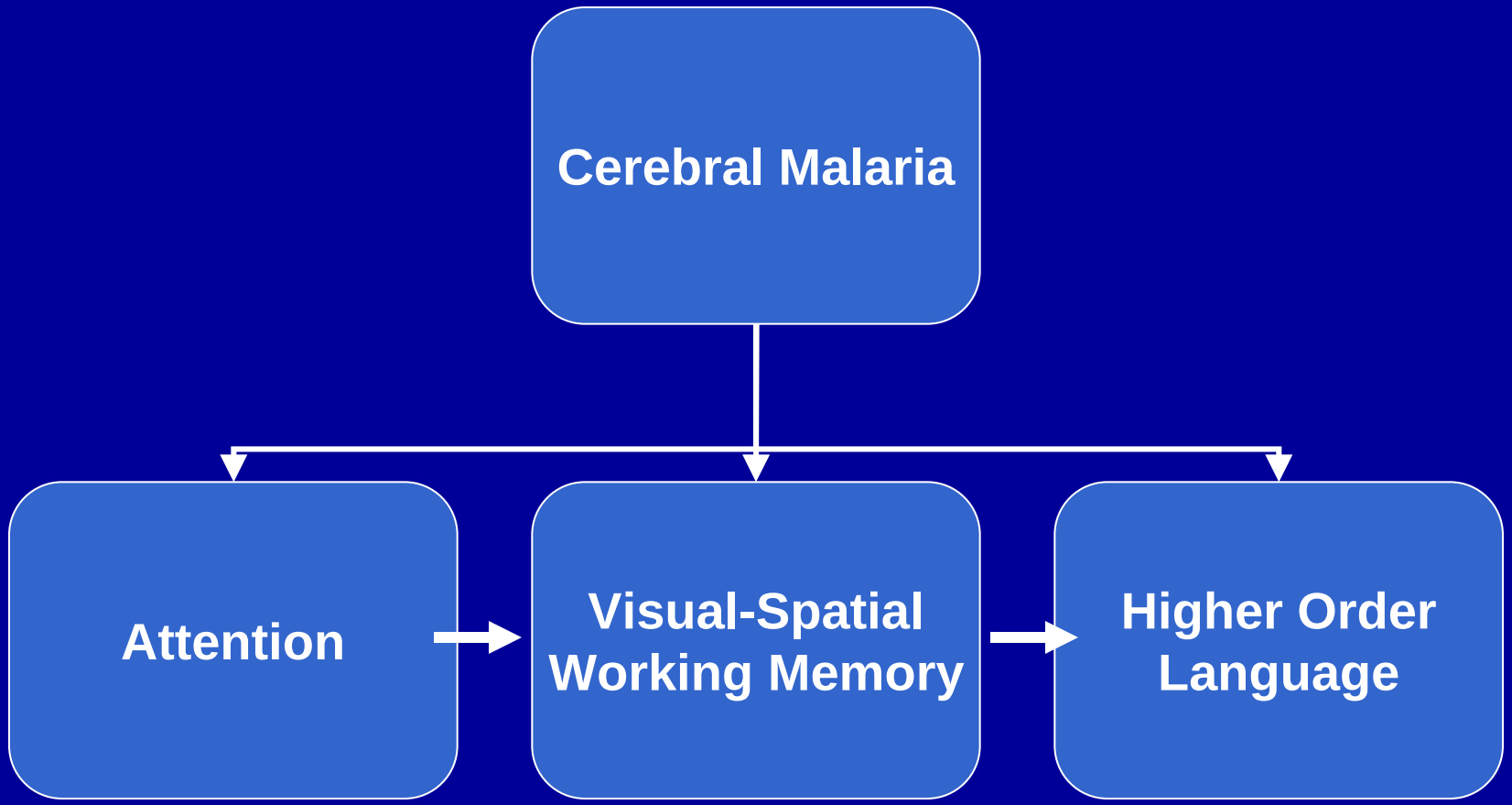
ABUBAKAR, A., HOLDING, P., NEWTON, C. R., VAN BAAR, A. & VAN DE VIJVER, F. J. (2009) The role of weight for age and disease stage in poor psychomotor outcome of HIV-infected children in Kilifi, Kenya. Dev Med Child Neurol, 51, 968-73.

Dr. Patrick Mutono malnutrition treatment program combined with MISC intervention: Kanginima Hospital, Pallisa District, Uganda

Quality of perinatal care and gestational and post-natal ART neurodevelopmental effects (incidence of early progressive encephalopathy)

Quality of Education, Effects of Education on Neuropsychological Outcomes

Neurocognitive Effects of Cerebral Malaria



CSF cytokines & cognitive deficits

- TNF-alpha levels correlated negatively with scores at 6 months in working memory (Spearman's rho, -0.32, P=0.06) and attention (Spearman's rho, -0.34, P=0.04).

John et al. (2008). Cerebrospinal fluid cytokine levels and cognitive impairment in cerebral malaria. *American Journal of Tropical Medicine and Hygiene*, 78(2), 2008, pp. 198-205.

KABC-2, TOVA-v, CogState, CBCL, BRIEF (pre and post training, 1 yr follow-up)

Captain's Log CCRT Training, Active Control (scrambled levels), Passive Control

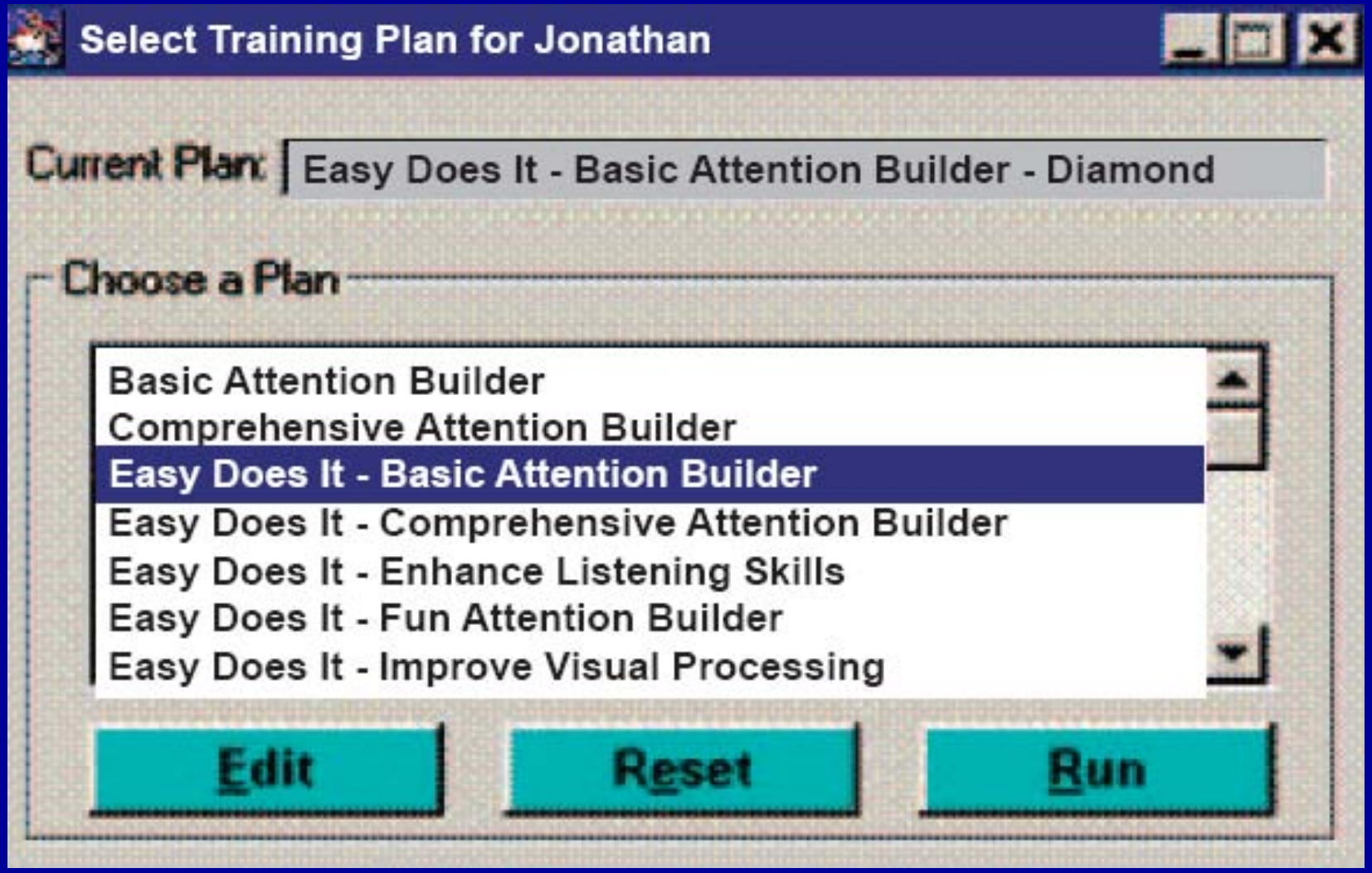
CM: 24 sessions (over 8 weeks)

"Spock's Brain"

The Enterprise is raided by an alien force, who steal Spock's brain, leading Kirk and McCoy in a desperate race to retrieve it.

Captain's Log CCRT Intervention

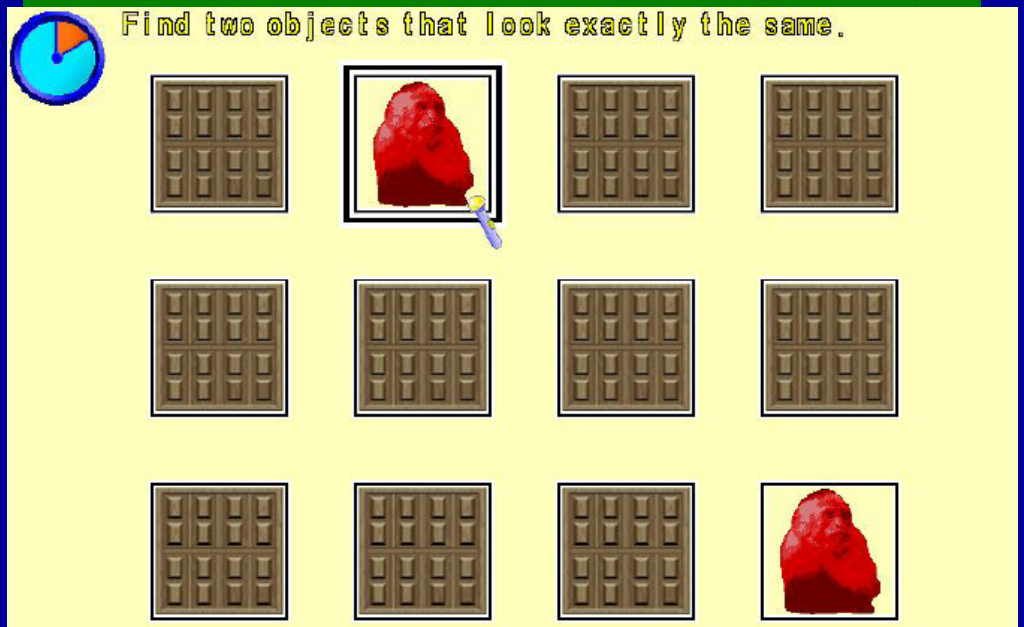
www.braintrain.com

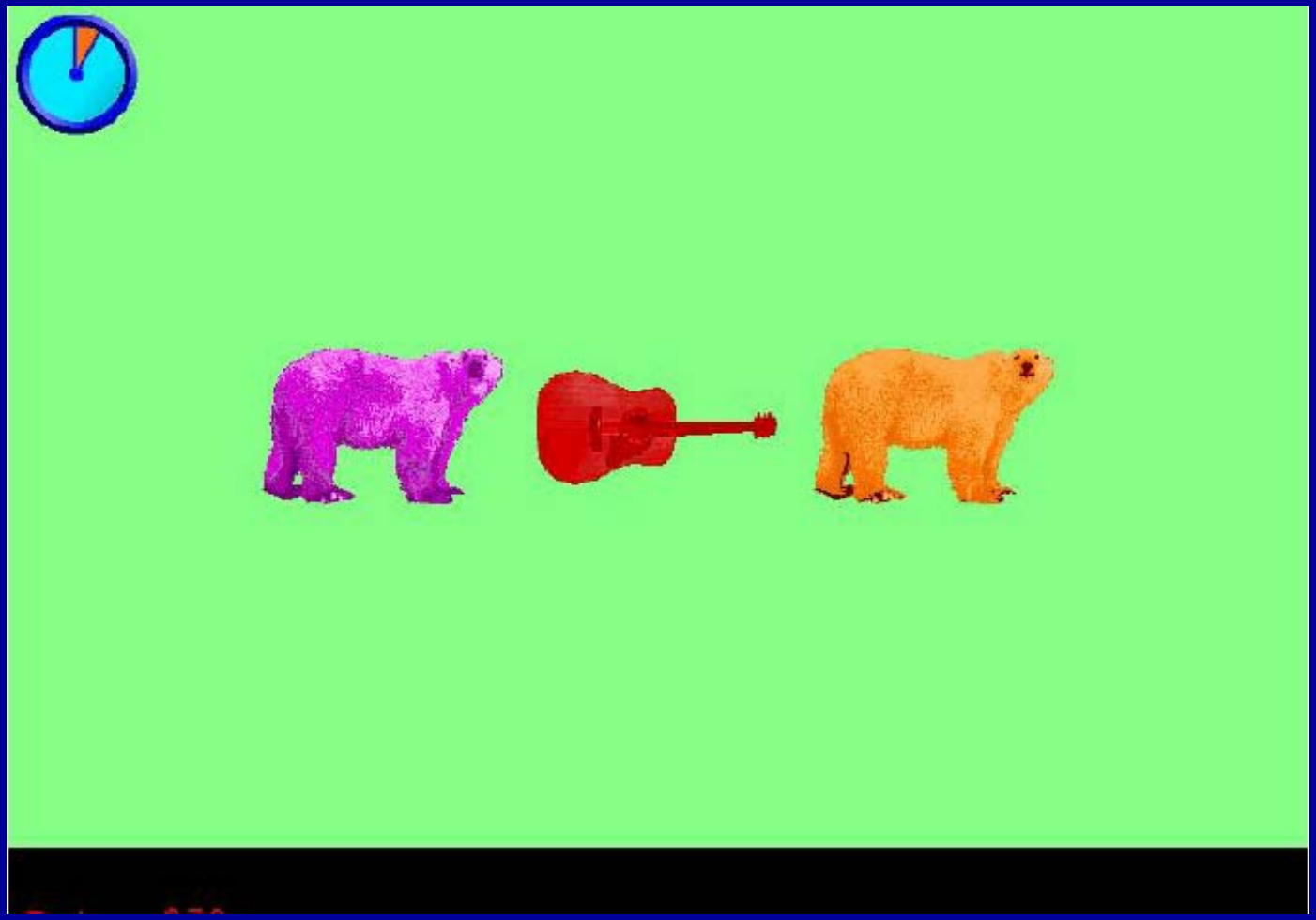


Concentration - 1 (Diamond/Medium)

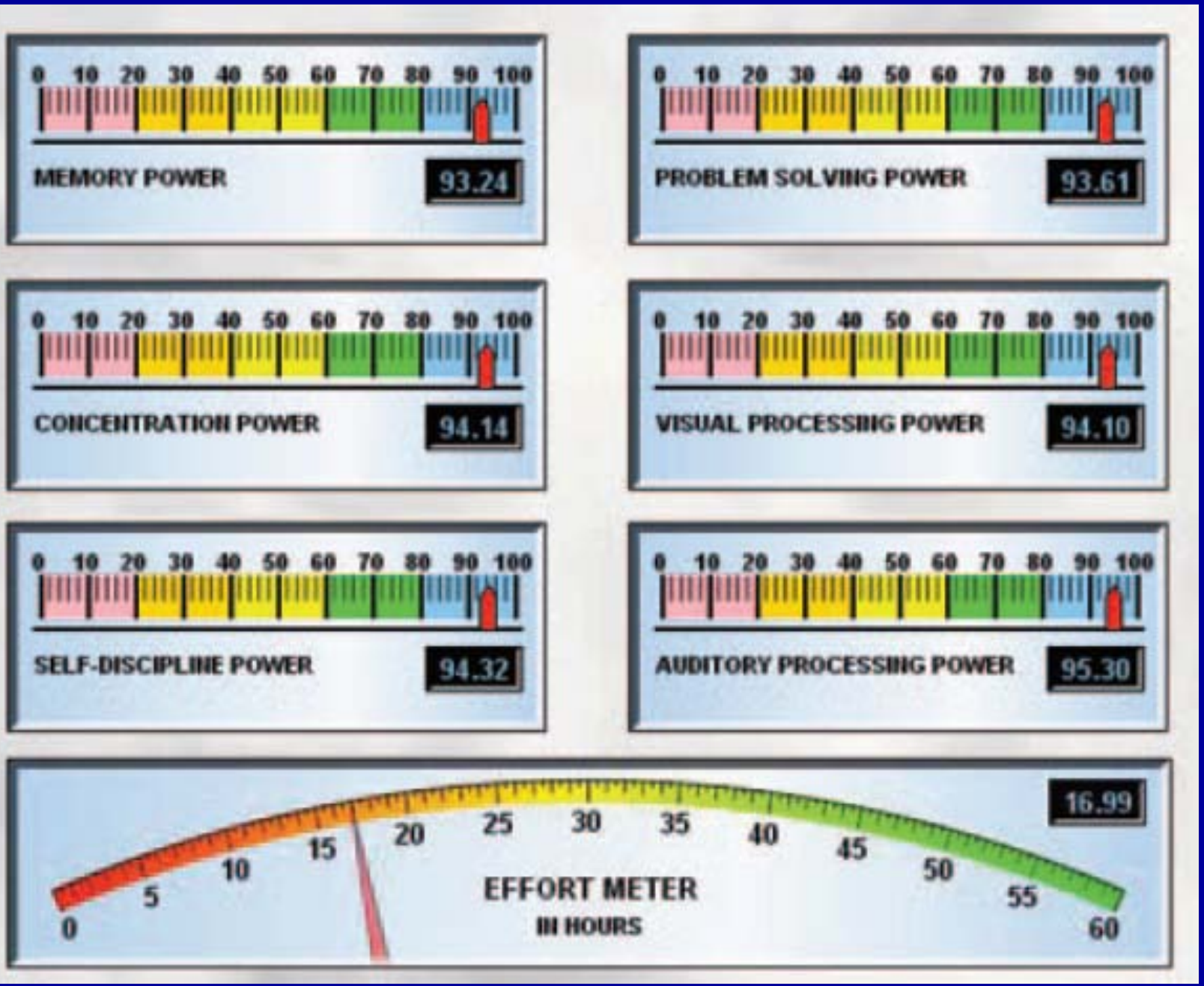
You will see a number of different objects. Each object has a match. Look carefully and find its exact match. Remember where the matches are located on the board. These objects will then be hidden behind some doors. Click on the doors to uncover each pair of objects that matches. If you do not find a match, then you must wait for the doors to close before making another choice. You must be both accurate and quick to win.

Exit | Say | Continue





Choose the item that doesn’t belong

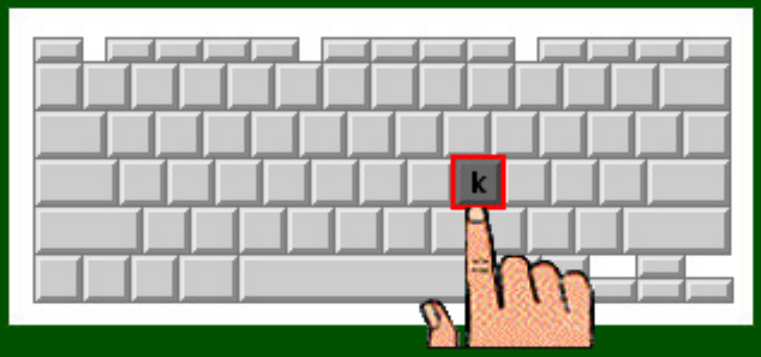

0 10 20 30 40 50 60 70 80 90 100
MEMORY POWER
93.24
0 10 20 30 40 50 60 70 80 90 100
PROBLEM SOLVING POWER
93.61
0 10 20 30 40 50 60 70 80 90 100
CONCENTRATION POWER
94.14
0 10 20 30 40 50 60 70 80 90 100
VISUAL PROCESSING POWER
94.10
0 10 20 30 40 50 60 70 80 90 100
SELF-DISCIPLINE POWER
94.32
0 10 20 30 40 50 60 70 80 90 100
AUDITORY PROCESSING POWER
95.30
0 5 10 15 20 25 30 35 40 45 50 55 60
EFFORT METER
IN HOURS
16.99

Detection (Simple Reaction Time)

Press YES as soon as a card turns face up.

Yes = K key.

Press Tab key to skip past demo.

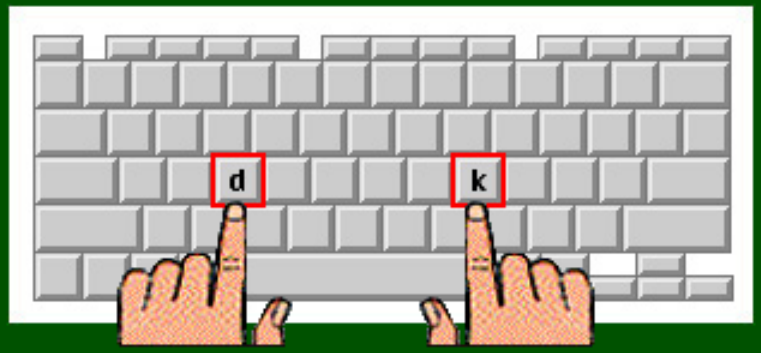


One-Back Matching Task (Working Memory)

Does the face-up card exactly match the one before?

Yes = K key.
No = D key.

Press YES key to begin.



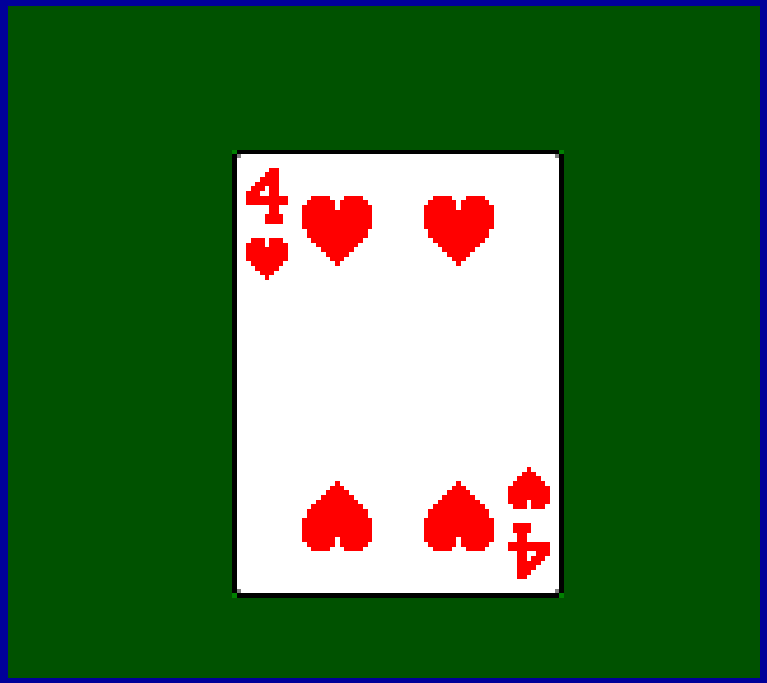
CogState design: Computer testing using playing card stimuli (culturally neutral, minimal language, game-like) www.cogstate.com

Is it there? **(detecting)**

Is it red ? **(identifying)**

Is it the same as the one before? **(working memory)**

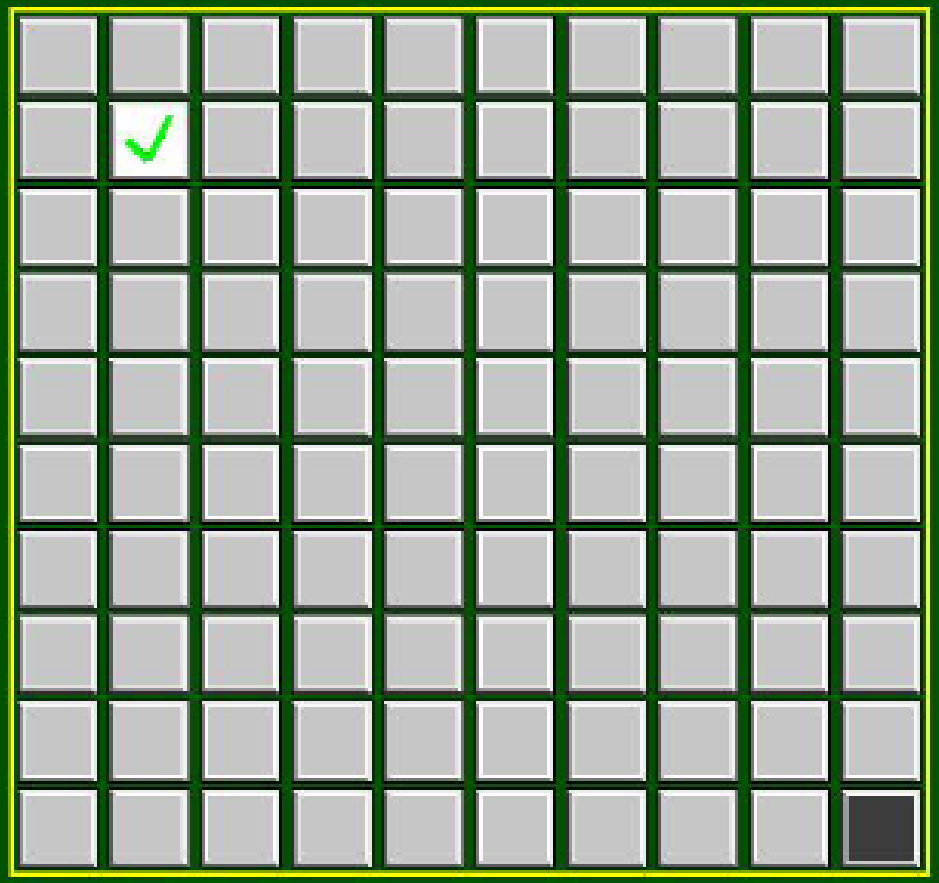
Was it already presented? **(memory)**



- Measures the speed, accuracy and consistency of responses
- Little practice effect.
- Sensitivity but not specificity,
- Good scientific validation

Tap on the tiles to find the hidden pathway.

Start at the top left and move one tile at a time.



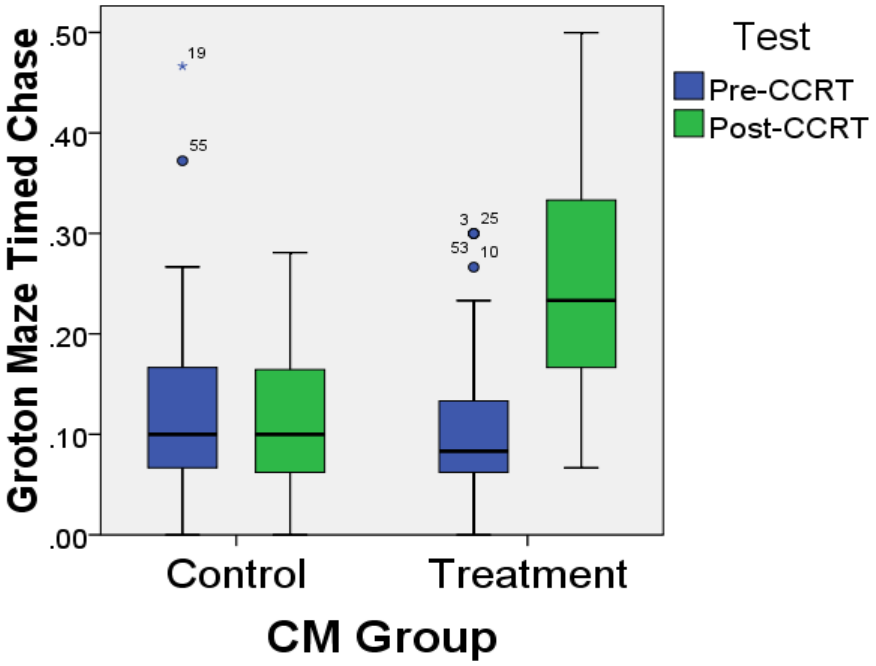
Groton Maze Chase Task

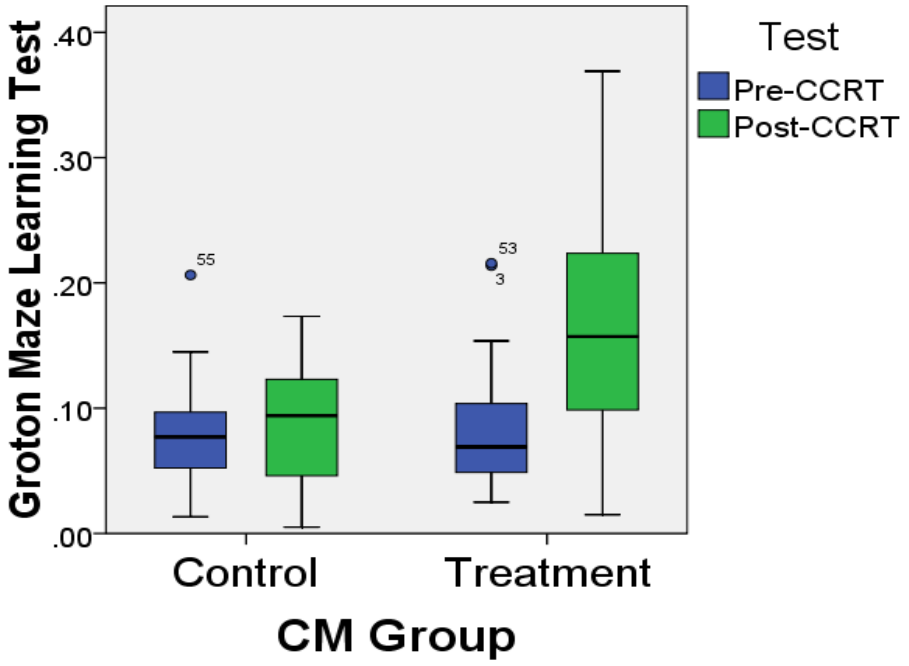
- The subject is shown a 10 x 10 grid of tiles on a computer touch screen.
- Tap the blue tile in the top left corner of the grid with the stylus pen.
- As the target moves, ***“chase”*** it by tapping on the tiles one at a time.
- Repeat the same task for a timed period of 30 seconds.

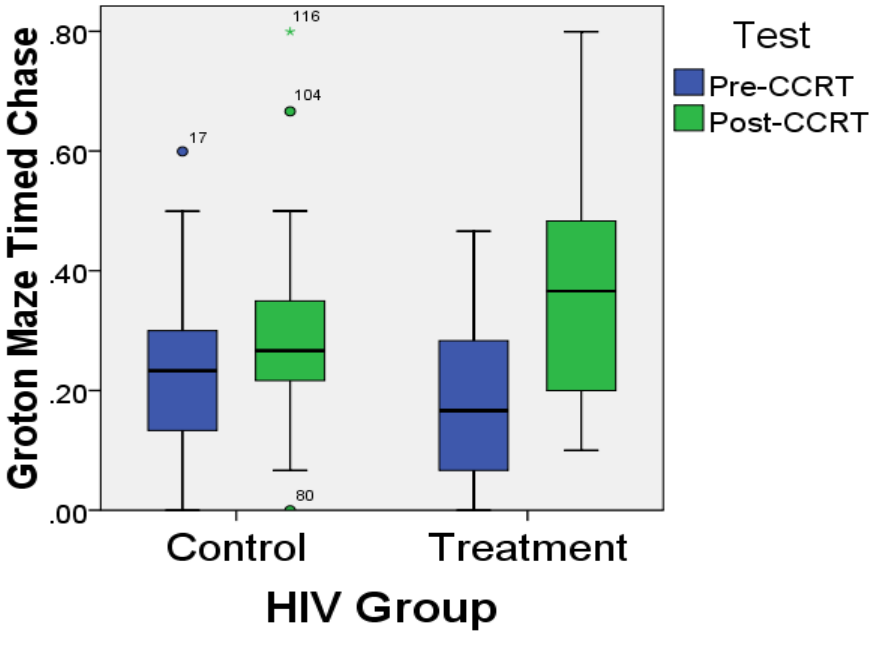
Groton Maze Learning Task

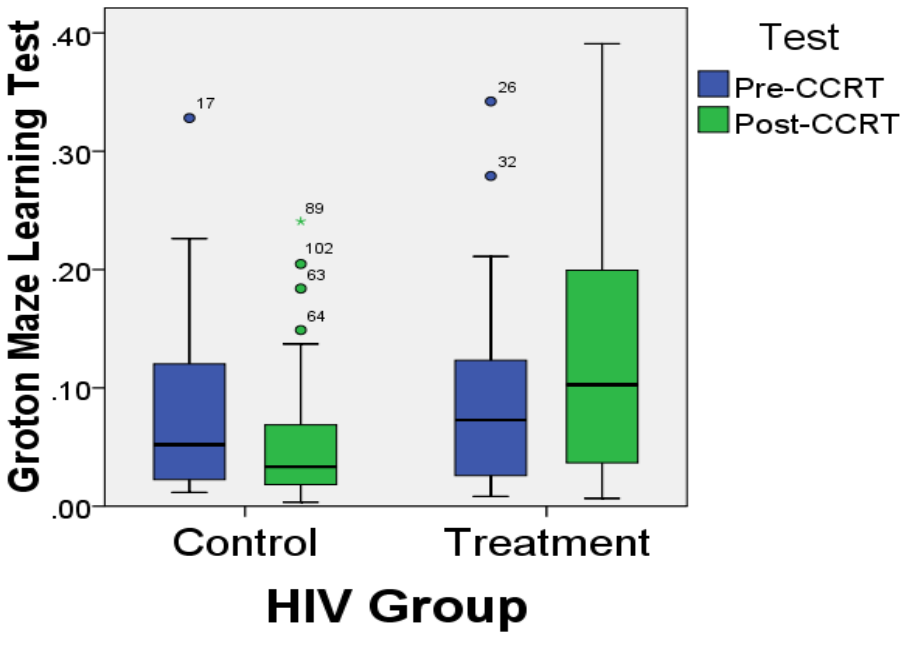
- The subject is shown a 10 x 10 grid of tiles on a computer touch screen.
- A 28-step pathway is hidden among these 100 possible locations.
- Move one tile at a time, toward the goal tile (bottom right).
- Trial-and-error learning of the 28-step pathway though the maze on the basis of step-by-step feedback (right or wrong move).

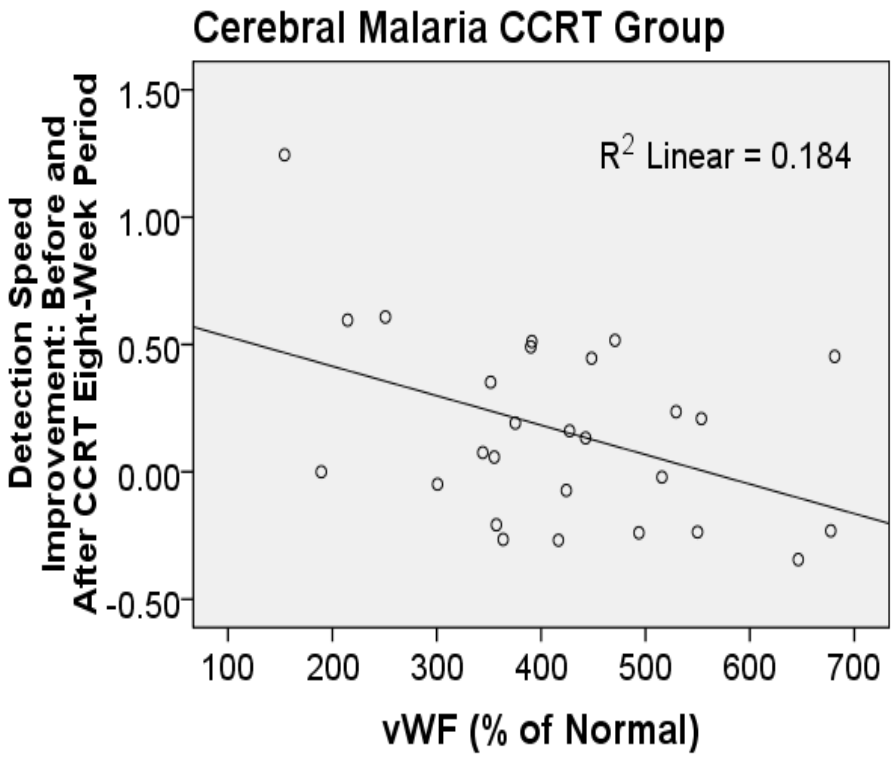
Box Plots of Correct Moves per Second on Groton Maze Tasks Pre- & Post-CCRT

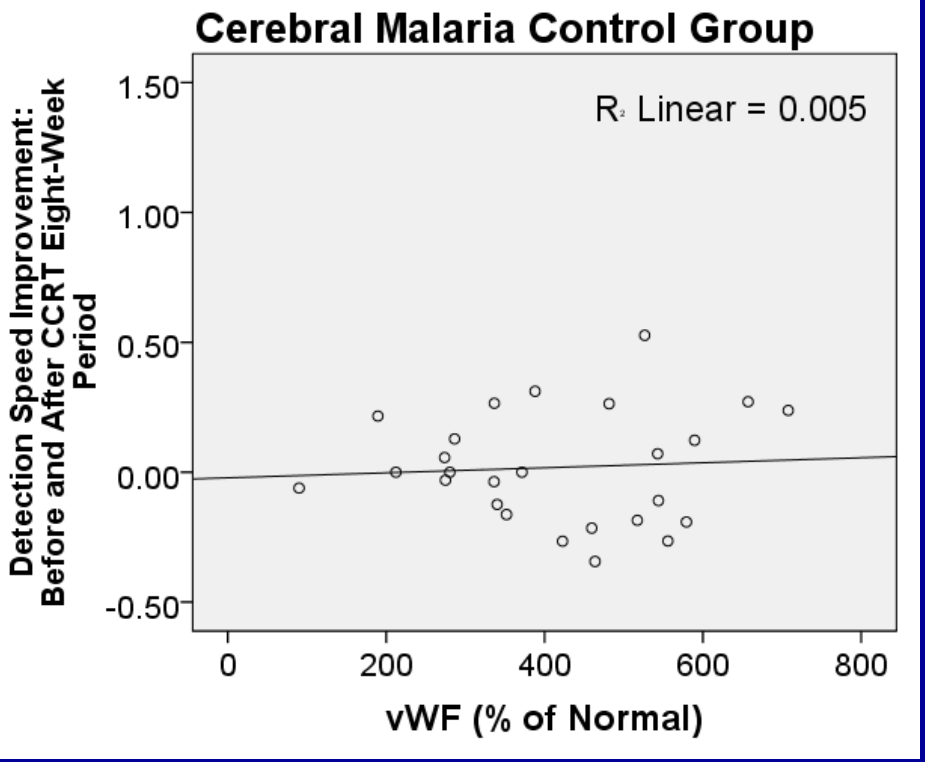






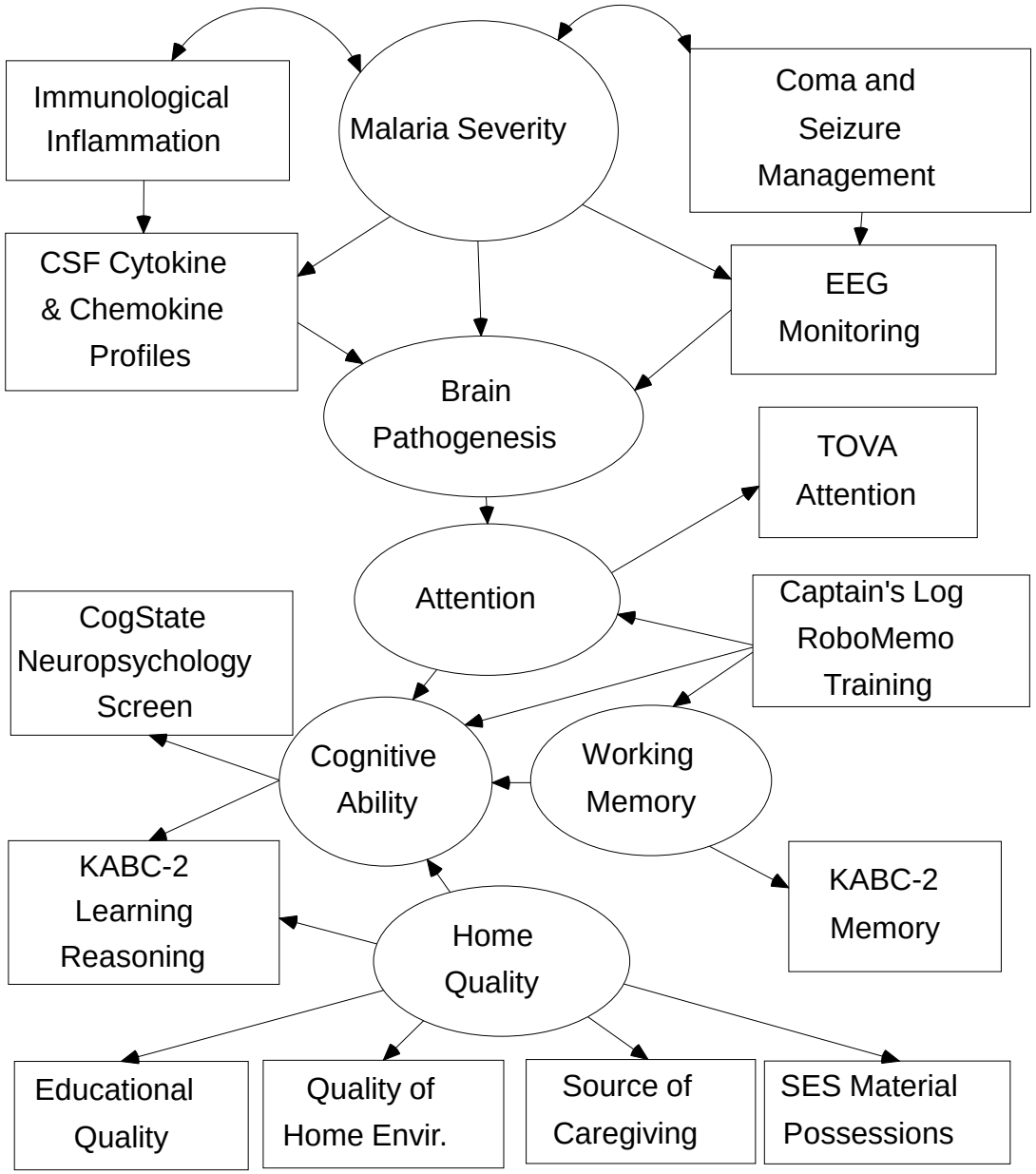






Correlation between von Willibrand Factor (vWF) level during acute CM illness and CogState card turn detection speed before and after CCRT training for intervention and control groups of CM survivors. (dynamic versus static neuropsychological outcomes).

Figure 6: Model of Neuropsychological Benefits of Captain's Log and RoboMemo Training for School-Age Malarial Children



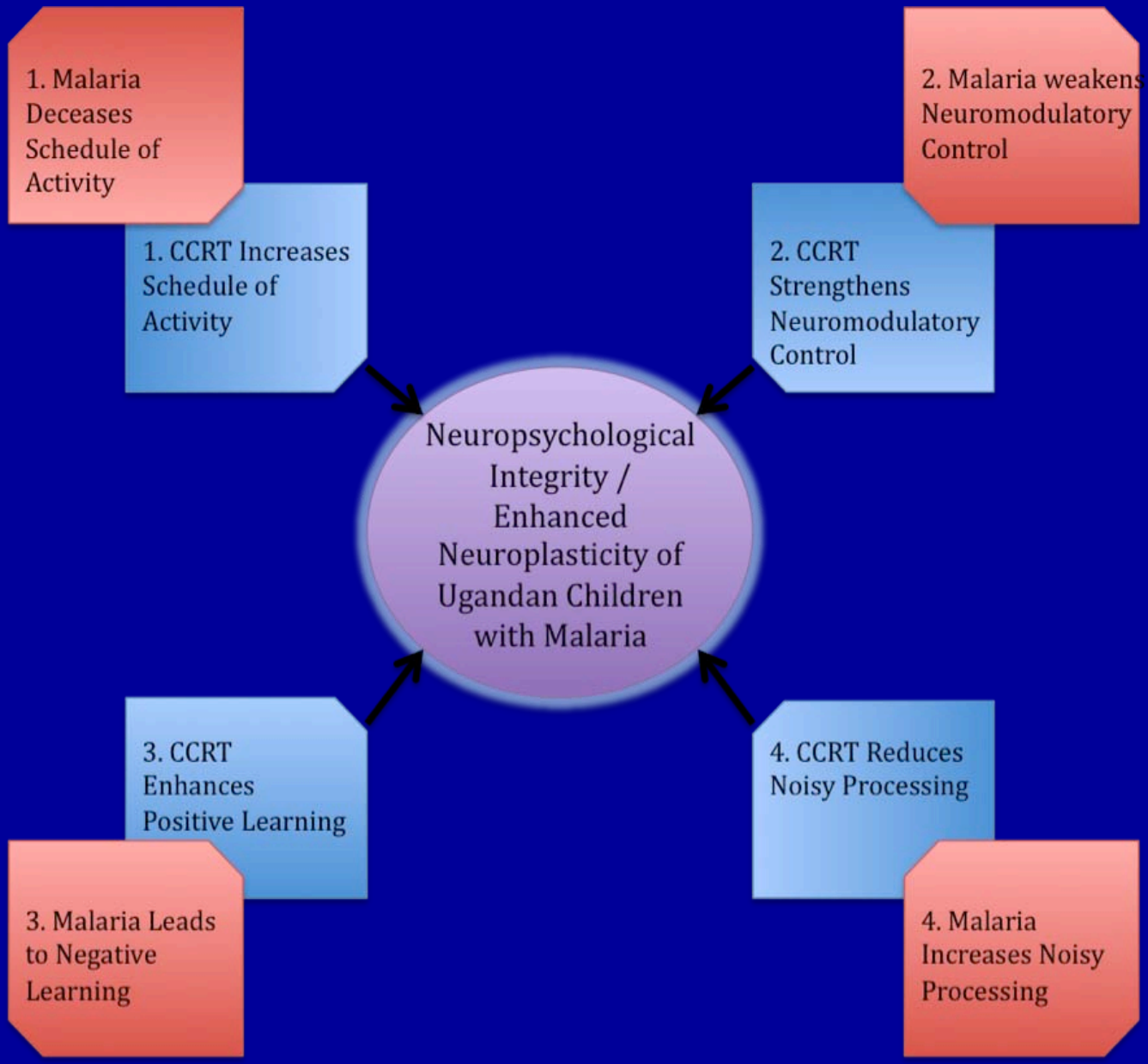


Figure 2. How CCRT remediates the root cause of functional decline in pediatric Malaria.

Follow-up Research Question

- Compared to Quinine, can Artesunate have stronger anti-inflammatory effects while treating complicated malaria during the acute phase of illness, reducing risk for neurological and neurocognitive sequelae? (monitor TNF-alpha, vWF, and other CSF cytokine and chemokine markers)

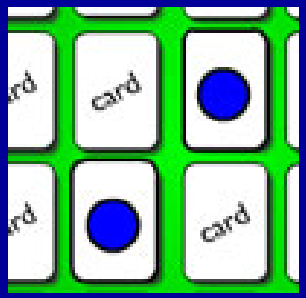
GENERALIBILITY OF PROTOCOLS

- *Assessment and Intervention* template for brain disorders in the developing world:
  - pathogenesis of infectious disease,
  - clinical and treatment factors, quality of home environment, and
  - subsequent neurocognitive outcomes
- Applicable to malaria, HIV, schistosomiasis, intestinal parasite infection and chronic anemia, and many other diseases.

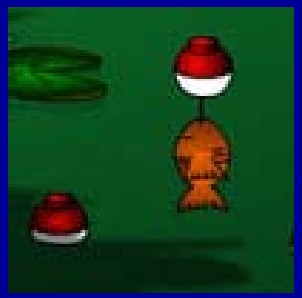
Students in the Andean village of Arahuay, Peru, using computers supplied by the organization One Laptop per Child. http://www.nytimes.com/2008/01/05/technology/05laptop.html

Professor Nicholas Negroponte of MIT has recently launched the “Give One Get One” (G1G1) campaign to provide inexpensive laptop XO computers (~ $200) with built in video, camera, and wireless capability.

Original Brain Powered Games: Professor Brian Winn, Director of MSU Games for Entertainment and Learning (GEL) laboratory



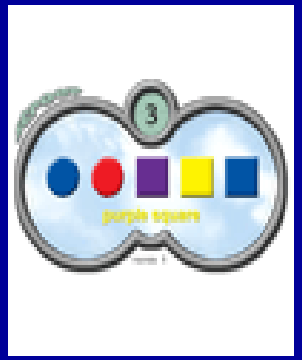
Matching



Gone Fishing

Leap Frog

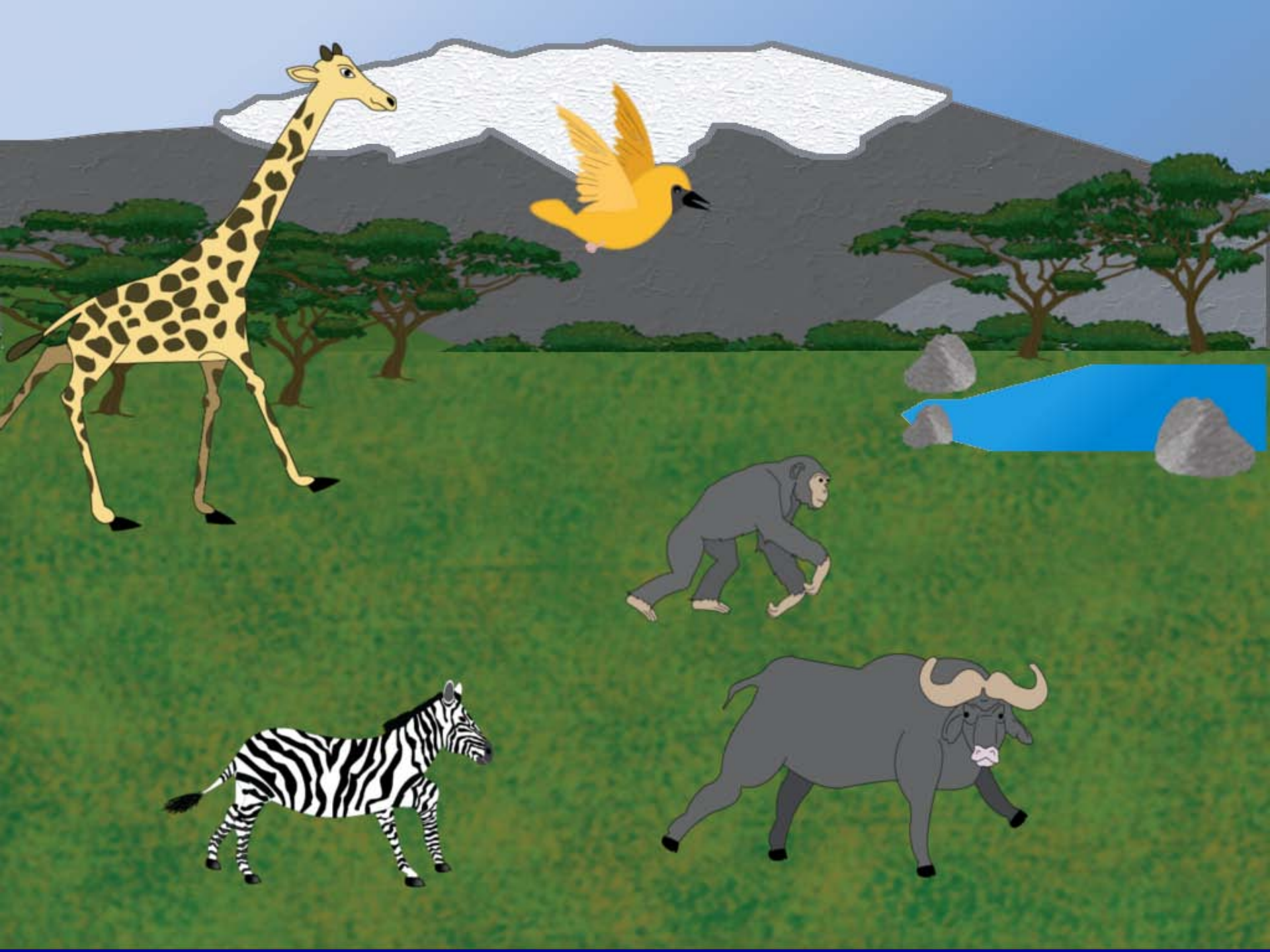
Hanoi Shipping



Stroop

Photo Flaw


New Round
Memorize everything now!
Round Count 2 - 10



Neuropsychology of African Children: Risk and Resilience (Boivin & Giordani, Eds.) Springer Publishing Series on Cross-Cultural Neuropsychology (Elaine Fletcher-Janzen, Ed.) Publication Release March, 2013.

Introduction: The Neuropsychology of African Children within a Co-Constructivist Paradigm
Michael J. Boivin, Hailey Wouters, and Bruno Giordani

Approaches to Assessment of Very Young Children in Africa in the Context of HIV
Betsy Kammerer, Peter Isquith, and Shannon Lundy

Acknowledging Methodological Complexity in Assessing Children in HIV-affected Communities in KwaZulu-Natal Province, South Africa
JD Kvalsvig, M Taylor, S Kauchali, and M Chhagan

Cognitive, Motor and Behavioral Development of Orphans of HIV/AIDS in Institutional Contexts
Kim T. Ferguson and Melody J. Lee

Factors Contributing to the Psychosocial Adjustment of Ugandan Preschool Children with HIV/AIDS
Rachelle A. Busman, Connie Page, Evelyn Oka, Bruno Giordani, and Michael J. Boivin

Examining the Psychosocial Adjustment and School Performance of Ugandan Children with HIV/ AIDs
Rachelle A. Busman, Evelyn Oka, Bruno Giordani, and Michael J. Boivin

Screening for Neurodisability in Low-Resource Settings Using the Ten Questions Questionnaire
Erin E. Lorencz and Michael J. Boivin

Language Development in sub-Saharan Africa
Katie Alcock and Nuala Alibhai

Psychosocial Aspects of Malnutrition among African Children: Antecedents, Consequences, and Interventions
Amina Abubakar

Assessing the Effects of Maternal Anemia on Child Development in Benin
Florence Bodeau-Livinec, Michel Cot, Ghislain K. Koura, and Michael J. Boivin

The Assessment of Skill learning in African Children……
Esther Adi-Japha

The Assessment of Neuropsychological Outcomes in Pediatric Severe Malaria
Penny Holding and Michael J. Boivin

Computerized Cognitive Rehabilitation Therapy (CCRT) for African Children: Evidence for Neuropsychological Benefit and Future Directions.
Paul Bangirana, Michael J. Boivin, Bruno Giordani

Measurement of cognitive outcomes of at-risk children using Novelty Processing in rural Kenyan children
Michael Kihara

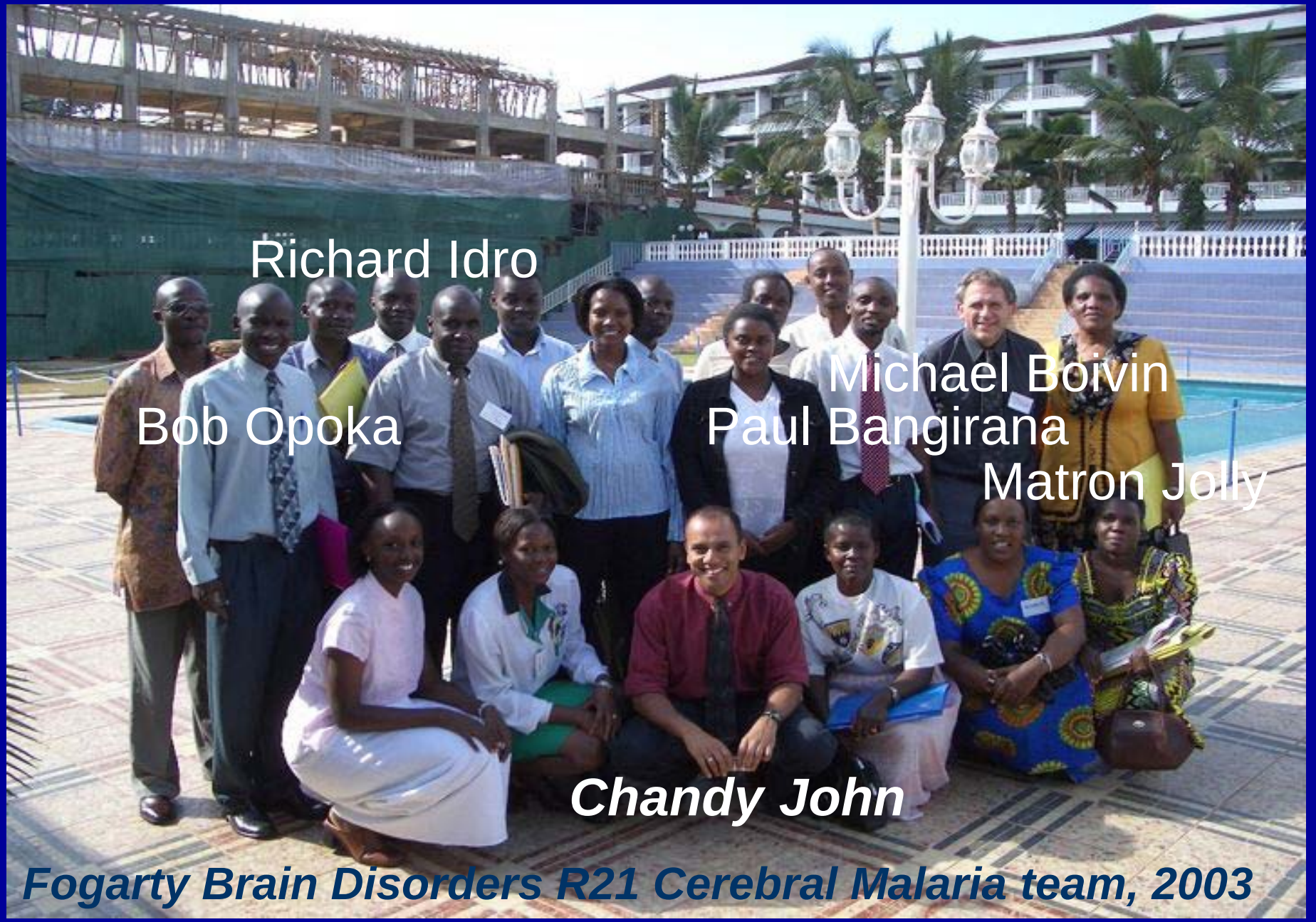
The Neuropsychology of Sickle cell Disease in West African Children
Nicolas Ruffieux and Claude-Alain Hauert

Postscript: Towards a Universal Brain/Behavior Omnibus in the Neuropsychology of African Children.
Michael J. Boivin, Karen Dobias, and Bruno Giordani

Final Thought

“Some . . . see things as they are and say why - I dream **things** that never were and **say why** not.”

George Bernard Shaw



Fogarty Brain Disorders R21 Cerebral Malaria team, 2003

Uganda: Something no other Fogarty site has!

Questions?

Correspondence can be directed to boivin@msu.edu

Figure 1: CM patient with retinal whitening in the central macula and subtle orange discoloration of the blood vessels

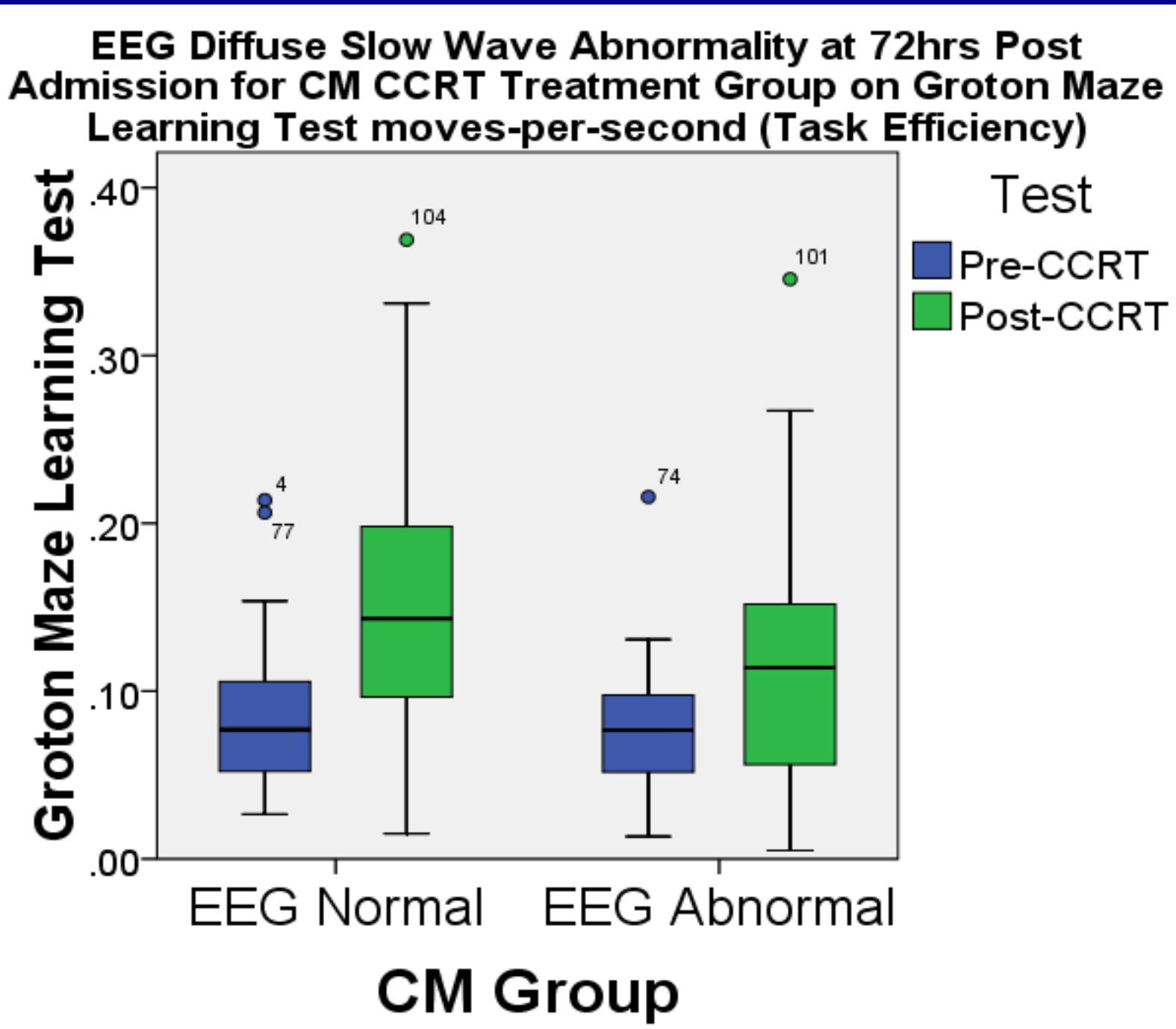
Birbeck et al., *Am J Trop Med Hyg*, Feb 2010; 82: 231 - 234.

Figure 2: CM patient with several features of CM retinopathy including macular and peripheral retinal whitening, hemorrhages, and papilledema

Birbeck et al., *Am J Trop Med Hyg*, Feb 2010; 82: 231 - 234.

Figure 4: Vessel whitening typical of CM retinopathy, with involvement of the capillary bed as well as larger retinal vessels. Retinal whitening is also seen.

Birbeck et al., *Am J Trop Med Hyg*, Feb 2010; 82: 231 - 234.


EEG Diffuse Slow Wave Abnormality at 72hrs Post Admission for CM CCRT Treatment Group on Groton Maze Learning Test moves-per-second (Task Efficiency)
Groton Maze Learning Test
.40
.30
.20
.10
.00
104
101
4
77
74
Test
Pre-CCRT
Post-CCRT
EEG Normal
EEG Abnormal
CM Group

Click if you see 2 or more coins.





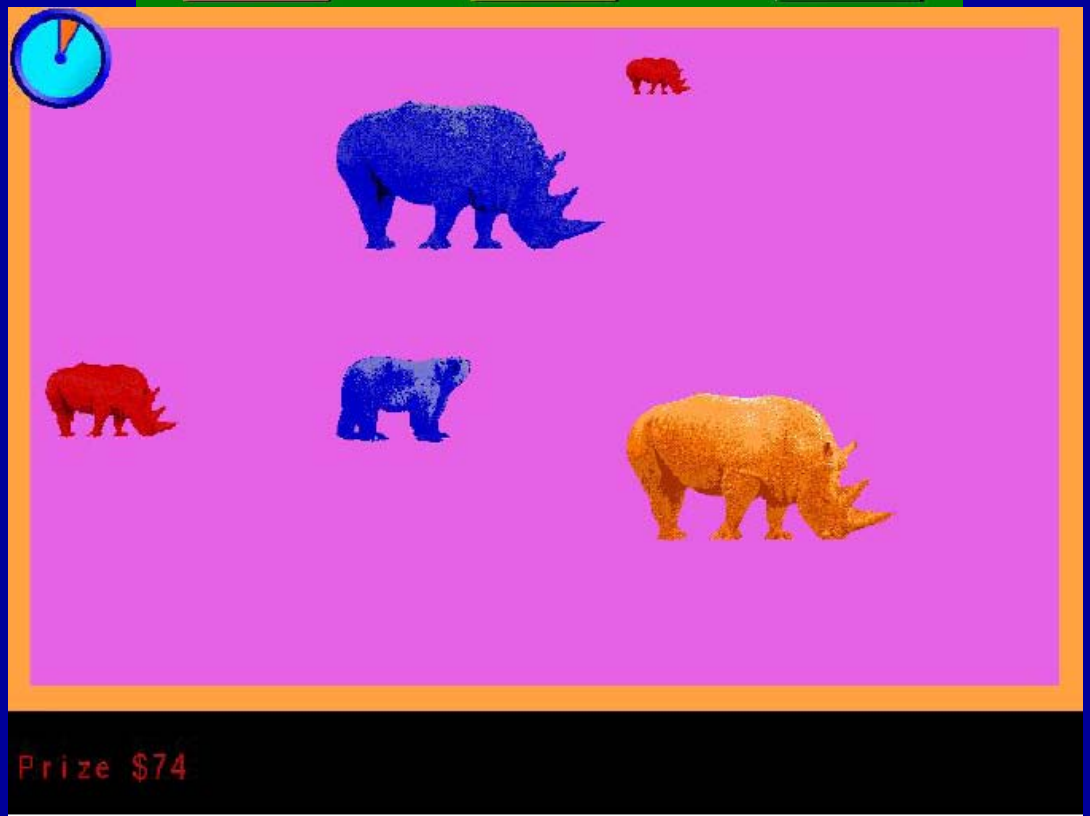



Prize $35

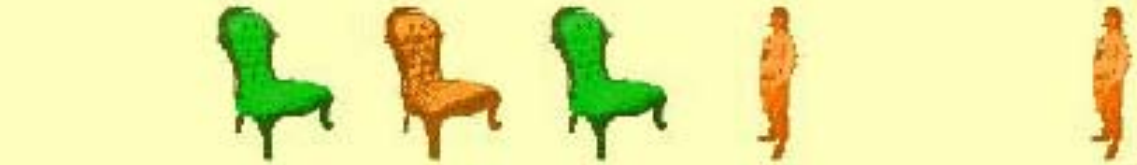
Mouse Hunt - 1 (Diamond/Medium)

Watch the pictures of the bears and rhinos. When one appears that is the SAME color as the border, click the mouse as quickly as you can.

Exit | Say | Continue



Find the missing image.



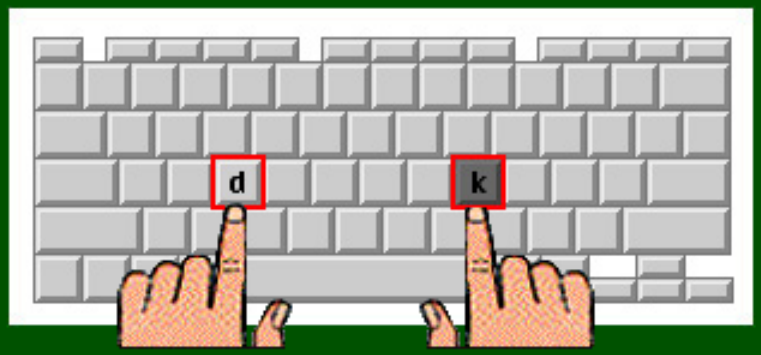
Prize $50

Identification: Choice Reaction Time

Is the face-up card red?

Yes = K key.
No = D key.

Press Tab key to skip past demo.



Any-Back Matching Task (Memory and Learning)

Have you seen this card before in this task?

Yes = K key.
No = D key.

Press Tab key to skip past demo.

Are there risks to participants from Captain’s Log CCRT?