Computerized Cognitive Assessments

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Harvard Medical School
Disclosures

• Consulting and Advisory Boards
  • Biogen Idec
  • Digital Cognition Technologies
  • Neurotrack
Times Have Changed!

Mainframe computers circa 1970

First Apple PC – circa 1984

VT 180 with external disc drive - 1982

First IBM PC - 1981
HISTORY OF PORTABLE DEVICES
Can we use technology to measure cognition?
The continuum of Alzheimer’s disease

Asymptomatic

Early symptomatic

Preclinical

“Normal” Aging

MCI

Dementia

Cognitive function

Years

Sperling R et al Alzheimer & Dementia 2011
Hypothetical Model of Emergence of Biomarkers and Cognitive Test Sensitivity


Standardized Tests

Digital Tests
iPad Computerized Cognitive Composite (C3)

Stark, 2013
Rentz et al 2011
CogState, Ltd
Validity: The C3 is correlated with Conventional Paper and Pencil Tests

\[ r = 0.56, p < .001 \]

\[ r = 0.43, p = .004 \]

\[ r = -0.29, p = .05 \]

\[ r = -0.23, p = .14 \]

Rentz, et al, *JPAD*, 2016; Buckley, R. *JPAD* 2017
The feasibility of at-home iPad cognitive testing for use in clinical trials


95% completed a 7 of the 9 at-home tests successfully

At-home tests could act as a proxy for the supervised in-clinic measurements on the iPad

R² = 0.51, p < 0.0001

p = 0.36
Computerized Cognitive Testing for Use in Clinical Trials: A Comparison of the NIH Toolbox and Cogstate C3 Batteries

Richard Gershon, PhD
Molly Wagster, PhD
Sandra Weintraub, PhD

Picture Vocabulary Test
Pattern Comparison Processing Speed Test
Picture Sequence Test
Dimensional Change Card Sort Test (DCCS)
Flanker Test/inhibitory Control and attention
Computerized Cognitive Testing for Use in Clinical Trials: A Comparison of the NIH Toolbox and Cogstate C3 Batteries

R.F. Buckley¹,²,³,⁴, K.P. Sparks¹,⁵, K.V. Papp¹,²,⁵, M. Dekhtyar¹,⁵, C. Martin⁶, S. Burnham⁷, R.A. Sperling¹,²,⁵, D.M. Rentz¹,²,⁵

The NIHTB and C3 Learning and Memory factor were positively correlated with the PACC (r=0.49 and r=0.58 p<0.001). The C3 Learning and Memory was the only composite that classified subtle cognitive impairment and demonstrated the greatest sensitivity and specificity.

<table>
<thead>
<tr>
<th>Regression</th>
<th>OR (r) [CI95%]</th>
<th>ROC analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
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<tr>
<td>NIHTB-CB</td>
<td>2.2 (.05) [1.1, 5.4]</td>
<td>0.55</td>
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<tr>
<td>C3 Learning-Memory</td>
<td>3.7 (.003) [5.8, 844.5]</td>
<td>0.61</td>
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<tr>
<td>C3 Processing Speed Attention</td>
<td>0.85 (.66) [0.4, 1.8]</td>
<td>0.50</td>
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</tbody>
</table>

Blue = C3 Learning-Memory, Red = NIHTB-CB, Green = C3 Processing Speed-Attention
The Computerized Cognitive Composite (C3) in A4, an Alzheimer’s Disease Secondary Prevention Trial

K.V. Papp1,2, D.M. Rentz1,2, P. Maruff3,4, C.-K. Sun5, R. Raman5, M.C. Donohue5, A. Schembri6, C. Stark6, M.A. Yassa6, A.M. Wessels7, R. Yaari7, K.C. Holdridge7, P.S. Aisen5, R.A. Sperling1,2 on behalf of the A4 Study Team

Unadjusted

Adjusted for age, sex and education
Classic Clock Drawing Task

- The clock drawing test has continued to be used to detect frank impairment among clinical populations

WHAT IF YOU COULD DIGITALIZE IT?
Digital Biomarkers

- Refining our ability to easily identify at-risk individuals is critical to clinicians and to future clinical trials
- We explored whether a digital clock drawing test could detect biomarker abnormalities comparable to or better than traditional cognitive tests

Clinically normal and MCI participants
AUC for PACC = 0.954
AUC Digital Clock = 0.86
24% increase in diagnostic discriminability from hand scored clock

High Amyloid PET associated with clock drawing in clinically normal participants
AUC Digital Clock = 0.72
AUC for PACC = 0.63

Capturing Cognitive Changes at the Earliest Stage of Alzheimer's Disease: A New Approach
Dorene M Rentz, Kathryn V. Papp, Danielle Mayblyum, Justin Sanchez, Hannah Klein, Reisa Sperling & Keith Johnson
Capturing Cognitive Changes at the Earliest Stage of Alzheimer’s Disease: A New Approach
D M Rentz, K V Papp, D Mayblyum, J Sanchez, H Klein, R A Sperling & K A Johnson

In Review

<table>
<thead>
<tr>
<th>Category</th>
<th>Amyloid FLR</th>
<th>Entorhinal Tau</th>
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<tbody>
<tr>
<td>PACC</td>
<td>-0.100</td>
<td>-0.136</td>
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<tr>
<td>Digitized Clock Summary</td>
<td>Command + Copy -0.241**</td>
<td>-0.191*</td>
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<tr>
<td></td>
<td>Command</td>
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<td>Clock Face Circularity -0.199*</td>
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<td>Component Placement -0.257**</td>
<td>-0.070</td>
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<td></td>
<td>Vertical Spatial Arrangement -0.194*</td>
<td>-0.351**</td>
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<tr>
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<td>Drawing Size -0.193*</td>
<td>-0.108</td>
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</table>

Digital Clock was associated with High amyloid but not PACC
Digital Maze Completion Test: Design

Detects differences in decision-making

No Choice Maze

Decision points added

Choice Maze- same solution

Dana L. Penney, William Souillard-Mandard, Dana Mukusheva, Irina Orlovsky, Dorene M. Rentz, Jordan Jara, Randall Davis

Presented at AAIC 2017

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Results: *Difference* in Completion Time

![Bar Chart](image)

Difference in Completion Time
Choice vs No-choice

- **HC**
- **aMCI**
- **AD**

**Results:**

<table>
<thead>
<tr>
<th>Group</th>
<th>Difference in Completion Time (sec)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>HC</td>
<td></td>
<td>p=0.05</td>
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<tr>
<td>aMCI</td>
<td></td>
<td>p=0.005</td>
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<tr>
<td>AD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Future Directions: Boston Remote Assessment for Neurocognitive Health

• Designed specifically for preclinical AD to increase sensitivity to both subtle changes & AD-specific cognitive processes that show early decline;
• Designed to include tasks and stimuli more relevant to everyday life
• Study aimed to demonstrate feasibility and validity against paper and pencil tests
Single Timepoint Results: BRANCH is correlated with paper and pencil measures

- $r = 0.565$, $p < 0.001$
- $r = 0.388$, $p < 0.001$
Longitudinal learning curves as a clinical marker of a clinical trial intervention?
Summary

• Digitized technology and machine learning techniques can expose cognitive inefficiencies for completing a cognitive task.

• Nuanced performances may become more important than tests that only disclose a total score or time to completion.
Future Directions

• Digital tests and algorithms that are honed for early detection of cognitive decline have promise for triaging patients in the PCP setting and potential referral to clinical trials
  • These tests need to be simple, easy to administer, quick and provide accurate diagnostic information

• Need to create digital applications that can capture change that is clinically meaningful i.e., capturing real life information

• Tests will still need to be psychometrically sound and demonstrate reliability
Funding: This study was supported by NIH grants Harvard Aging Brain Study (2P01AG036694-06, PI: Sperling, Johnson) a supplement to the Harvard Aging Brain Study (PI: Rentz), Massachusetts ADRC Pilot Award (Papp, Amariglio)