Role of Computerized Screening in Healthcare Teams: Why Computerized Testing is NOT the Death of Neuropsychology

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Cleveland Clinic

INS CE Workshop, February 15, 2018
Conflicts of Interest

Dr. Rao has received royalties from the Cleveland Clinic for licensing MSPT-related technology. In addition, Dr. Rao has received honoraria, royalties, or consulting fees from Biogen, Genzyme, and Novartis and research funding from Biogen and Novartis.
Introduction

• Many neuropsychologists view computerized testing as a threat to their clinical practice.
• Physician referrals for neuropsychological assessments replaced by computerized neuropsychological examinations that provide meaningful clinical interpretations.
• No doubt, in some settings, this concern is valid.
• However, computerized testing has the capability of expanding clinical neuropsychological services to a broader range of patients in a wider range of clinical settings.
Rationale for Computerized Screening

• Premise: an extraordinarily large number of patients who require neuropsychological services are simply not identified by current healthcare practices.
• Unlike blood pressure or weight, cognition is rarely measured during routine medical visits.
• Growing interest in integrated care and a shift to a population health based reimbursement model in the US.
• With this, an increased need for reliable, valid cognitive screening measures incorporated seamlessly into a standard medical visit with minimal disruption of service delivery flow or need for additional personnel.
Goals of Workshop

• Briefly outline our 4-year experience with the development and implementation of neuropsychological screening assessments administered via an iPad.

• Development team consisted of clinical neuropsychologists, neurologists, biomedical engineers, computer scientists, and clinical and administrative support staff.

• Provide two illustrative examples:
  • Routine clinical screening of patients with multiple sclerosis
  • Routine cognitive screening of primary care patients to identify older persons in the preclinical stage of Alzheimer’s disease.
Application to Multiple Sclerosis
[In] most of the patients affected by multi-locular sclerosis whom I have had occasion to observe … there is marked enfeeblement of the memory; conceptions are formed slowly; the intellectual and emotional faculties are blunted … It is not rare to see them give way to foolish laughter for no cause and sometimes to melt into tears without reason.

Charcot (1877)
# PREVALENCE OF COGNITIVE DYSFUNCTION IN MULTIPLE SCLEROSIS

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Smedt et al., 1984</td>
<td>46</td>
<td>65</td>
</tr>
<tr>
<td>Parsons et al., 1957</td>
<td>17</td>
<td>65</td>
</tr>
<tr>
<td>Rao et al., 1984</td>
<td>44</td>
<td>64</td>
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<tr>
<td>Staples &amp; Lincoln, 1979</td>
<td>64</td>
<td>60</td>
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<td>Lyon-Caen et al., 1986</td>
<td>30</td>
<td>60</td>
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<tr>
<td>Heaton et al., 1985</td>
<td>100</td>
<td>56</td>
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<tr>
<td>Bertrando et al., 1983</td>
<td>22</td>
<td>55</td>
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<tr>
<td>Peyser et al., 1986</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>Rao et al., 1991</td>
<td>100</td>
<td>43</td>
</tr>
</tbody>
</table>
COGNITIVE DYSFUNCTION IN MS

Prevalence of Impairment by Cognitive Domain*

Impact of Cognitive Dysfunction on Daily Functioning

Cognitively intact (n=52)
Cognitively impaired (n=48)

- Work status: $P<0.01$
- Social activity: $P<0.05$
- Personal assistance: $P<0.01$
- Community services
- Financial status
- Transportation
- Personal residence

ASSESSMENT OF COGNITIVE DYSFUNCTION

• MS Functional Composite (Cutter et al., 1999)
  • 3 measures (includes PASAT)
  • used as outcome measure in clinical trials
  • administered and scored by non-neuropsychologist

• Neuropsychological Screening Battery (Rao et al., 1991)
  • 20-25 minutes to administer
  • used to screen patients in clinical setting

• Comprehensive Neuropsychological Examination
  • 3-5 hours, addresses differential diagnosis, disability questions
  • administered/interpreted by board-certified clinical neuropsychologist
## Multiple Sclerosis Functional Composite (MSFC)

<table>
<thead>
<tr>
<th>Function Evaluated</th>
<th>Test</th>
</tr>
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<tbody>
<tr>
<td>Cognition</td>
<td>PASAT-3*</td>
</tr>
<tr>
<td>Hand/eye coordination (avg. of right and left hands)</td>
<td>9-Hole Peg Test†</td>
</tr>
<tr>
<td>Leg/ambulation</td>
<td>Timed 25-Foot Walk‡</td>
</tr>
</tbody>
</table>

*Measures the number of correct answers; †Time to insert and remove 9 pegs; ‡Time taken in seconds.

New Developments

NINDS Common Data Elements (2011) – Cognition in MS

- Cognitive Subcommittee Panel: L Krupp, G Francis, S Rao, N LaRocca, D Langdon, RHB Benedict (Chair)
- Preliminary Recommendations:
  - Core CDE: Symbol Digits Modalities Test
  - Supplemental Tests:

<table>
<thead>
<tr>
<th>Test</th>
<th>Domain</th>
<th>Time</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT2 Learning Trials 1-5</td>
<td>auditory/verbal memory</td>
<td>10 min</td>
<td>Primary</td>
</tr>
<tr>
<td>BVMTR Learning Trials 1-3</td>
<td>visual/spatial memory</td>
<td>05 min</td>
<td>Primary</td>
</tr>
<tr>
<td>Rao PASAT 3.0 ISI</td>
<td>processing speed and working memory</td>
<td>05 min</td>
<td>Secondary</td>
</tr>
<tr>
<td>DKEFS Sorting Test</td>
<td>executive function</td>
<td>10 min</td>
<td>Secondary</td>
</tr>
<tr>
<td>CVLT2 Learning Delayed Recall</td>
<td>auditory/verbal memory</td>
<td>10 min</td>
<td>Primary</td>
</tr>
<tr>
<td>BVMTR Learning Delayed Recall &amp; Copy</td>
<td>visual/spatial memory</td>
<td>05 min</td>
<td>Primary</td>
</tr>
<tr>
<td>COWAT</td>
<td>executive function</td>
<td>05 min</td>
<td>Primary</td>
</tr>
</tbody>
</table>
Symbol Digit Modalities Test (SDMT)*

KEY

\[
\begin{array}{cccccccc}
( & - & l & - & > & + & ) & \div \\
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9
\end{array}
\]

Why Switch from PASAT to SDMT?

- Faster administration time (SDMT = 3 min.; PASAT = 6 min)
- Easier to administer (SDMT – stimuli on piece of paper; PASAT requires CD player)
- Multiple alternate, equivalent test versions developed to minimize practice effects
- SDMT tolerated better by MS patients than PASAT
- Can be more readily adapted for computerized testing than PASAT (e.g., iPad app)
Why Switch from PASAT to SDMT?

- Excellent reliability\(^1\)-\(^2\), discriminative validity\(^3\)-\(^7\), and fair to good predictive validity in MS patients\(^8\)-\(^{11}\)
- SDMT cut-off scores identify clinically meaningful change (e.g., 4-5 point drop associated with clinical relapse\(^{10}\) or losing capacity to work over five years\(^9\))
- Correlates as well as PASAT with T2 lesions and atrophy\(^8\)
- Many RCTs have used PASAT as part of MSFC; both tests likely to be administered in future trials

Inefficiency in Assessing Cognition in the MS Clinic

- Despite the high prevalence of cognitive dysfunction in MS (>50%) and its dramatic impact on quality of life, comprehensive MS care centers rarely screen for cognitive dysfunction using objective neuropsychological tests.
- Self-report and physician assessment of cognitive dysfunction is inaccurate.
- Many MS patients do not get appropriate referrals for comprehensive neuropsychological examinations.
Multiple Sclerosis Performance Test (MSPT): An iPad®-based assessment tool

- Fully integrated medical device designed with software and hardware components
- Designed to objectively quantify the major cognitive, motor, and visual symptoms and quality of life outcomes associated with MS
- Comprises
  - A structured patient history
  - The Neurological Quality of Life (Neuro-QoL) assessment
  - An electronic adaptation of the MS functional composite (MSFC)

*The MSPT is self-administered*

Developed by Cleveland Clinic neurological institute and biomedical engineering collaboration, the MSPT has been in use at the Mellen Center since September 2015
The MSPT collects a structured history and patient-reported outcomes:

- **MyHealth**: Demographic, MS history and treatment information questionnaire
- **Neuro-QoL**: Health-related quality-of-life questionnaire for people with neurological disorders
Neuroperformance assessment modules are electronic adaptations of the Multiple Sclerosis Functional Composite.
The Processing Speed Test assesses cognitive function

- Patients are asked to match symbols and numbers according to the key provided.
- Symbols are presented one row at a time, and patients are asked to enter the correct numbers as quickly and accurately as possible.
- The assessment score is the number of correct responses obtained in 2 minutes.
The Contrast Sensitivity Test measures visual acuity

- Patients are asked to identify letters of different size and contrast, 100% and 2.5%, on the MSPT display.
- The distance of the patient’s head from the screen is continuously monitored using the front-facing iPad camera.
- The assessment score is the number of letters correctly identified at 2.5% contrast.
  - The total possible number of correct letters is 60.
The Manual Dexterity Test assesses upper extremity function

- Patients are asked to move each peg, one at a time, from the bottom row to the upper holes in the peg board. Without pausing, they then move the pegs back to the bottom row.
- Patients will complete the test with each hand once.
- The assessment score is the number of seconds patients take to complete the assessment.
  - Each hand is scored separately.
The Walking Speed Test is a measure of lower extremity function.

**Walking Speed Test**

- Patients are asked to walk 25 feet on straight, unobstructed and level ground.
  - It is at the discretion of the healthcare provider to determine if a patient is capable of completing the test and if assistance is required.
- Patients use a Bluetooth remote to indicate the beginning and end of the 25-foot walk.
- Patients may use their assistive device (cane, rollator, walker, etc) when doing this task.
- The assessment result is the number of seconds patients take to walk the 25-foot course.
Processing speed test: Validation of a self-administered, iPad®-based tool for screening cognitive dysfunction in a clinic setting

Stephen M Rao, Genna Losinski, Lyla Mourany, David Schindler, Bernadett Mamone, Christine Reece, Danielle Kemeny, Sridar Narayanan, Deborah M Miller, Francois Bethoux, Robert A Bermel, Richard Rudick and Jay Alberts
MS and HC Samples

<table>
<thead>
<tr>
<th>Variable</th>
<th>Substudy 1: test-retest reliability and practice effects</th>
<th>Substudy 2: sensitivity to MS and convergent validity</th>
<th>Substudy 3: correlations with MRI lesion load</th>
<th>Substudy 4: effects of technician presence/absence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HC (n=116)</td>
<td>MS (n=75)</td>
<td>HC (n=85)</td>
<td>MS (n=125)</td>
</tr>
<tr>
<td>Age—mean years, SD</td>
<td>42.5</td>
<td>11.9</td>
<td>44.9</td>
<td>9.4</td>
</tr>
<tr>
<td>Education—mean years, SD</td>
<td>15.6</td>
<td>2.6</td>
<td>15.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Gender—male, %</td>
<td>47</td>
<td>40.5</td>
<td>23</td>
<td>30.7</td>
</tr>
<tr>
<td>Disease duration—mean years, SD</td>
<td>--</td>
<td>--</td>
<td>11.3</td>
<td>8.2</td>
</tr>
<tr>
<td>Disease course—n, %</td>
<td>--</td>
<td>--</td>
<td>56</td>
<td>74.7</td>
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<tr>
<td>Relapsing remitting</td>
<td>--</td>
<td>--</td>
<td>16</td>
<td>21.3</td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>--</td>
<td>--</td>
<td>2</td>
<td>2.7</td>
</tr>
<tr>
<td>Primary progressive</td>
<td>--</td>
<td>--</td>
<td>1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

MS: multiple sclerosis; MRI: magnetic resonance imaging; HC: healthy controls; SD: standard deviation.
Test-Retest Reliability

Convergent Validity

## Practice Effects

<table>
<thead>
<tr>
<th>Group</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Paired $t$-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>HC ($n=116$)</td>
<td>58.3</td>
<td>11.1</td>
<td>62.2</td>
</tr>
<tr>
<td>MS ($n=75$)</td>
<td>51.1</td>
<td>11.9</td>
<td>52.8</td>
</tr>
<tr>
<td>Combined ($n=191$)</td>
<td>55.5</td>
<td>12.0</td>
<td>58.5</td>
</tr>
</tbody>
</table>

PST: Processing Speed Test; MS: multiple sclerosis; HC: healthy controls; SD: standard deviation.
Correlation with T2 Lesions

SDMT

PST

Number Correct

T2 Lesion Load

Number Correct

T2 Lesion Load

rho = -0.25, p = 0.20

rho = -0.44, p = 0.02
Does a Technician Have to be Present to Obtain a Valid Assessment?

<table>
<thead>
<tr>
<th>Group</th>
<th>TP</th>
<th></th>
<th>TA</th>
<th></th>
<th>Difference (TP-TA)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC (n=24)</td>
<td>58.4</td>
<td>12.2</td>
<td>58.9</td>
<td>11.7</td>
<td>-0.5</td>
<td>0.691</td>
</tr>
<tr>
<td>MS (n=26)</td>
<td>49.7</td>
<td>14.3</td>
<td>50.8</td>
<td>13.6</td>
<td>-1.1</td>
<td>0.193</td>
</tr>
</tbody>
</table>

PST: Processing Speed Test; MS: multiple sclerosis; HC: healthy controls; SD: standard deviation; TP: technician present; TA: technician absent.
MSPT: Validation of Tests of Low Contrast Visual Acuity and Upper and Lower Motor Functions

Rachel Galioto, Megan Sokolowski, Marisa McGinley, Tanujit Dey, Lyla Mourany, David Schindler, Christine Reece, Malory Weber, Deborah M. Miller, Francois Bethoux, Robert A. Bermel, Richard Rudick, Glenn Phillips, Jane Rhodes, Jay Alberts and Stephen M. Rao

Submitted for publication
Test-Retest Reliability – Manual Dexterity Test

MDT DH: Healthy Controls
CCC = 0.63

MDT DH: Multiple Sclerosis
CCC = 0.84

MDT DH: Combined Groups
CCC = 0.81

MDT NDH: Healthy Controls
CCC = 0.71

MDT NDH: Multiple Sclerosis
CCC = 0.69

MDT NDH: Combined Groups
CCC = 0.71
Test-Retest Reliability – Contrast Sensitivity and Walking Speed Tests

CST: Healthy Controls
CST: Multiple Sclerosis
CST: Combined Groups

WST: Healthy Controls
WST: Multiple Sclerosis
WST: Combined Groups
Convergent Validity –
Manual Dexterity Test
Convergent Validity – Contrast Sensitivity and Walking Speed Tests
Sensitivity to MS –
All MS Patients (N = 1,062)

Note: Adjusted Z scores based on regression based norms (age, education, sec, and race) derived from 180 healthy subjects.
Sensitivity to MS – Related to Disease Duration

Note: Adjusted Z scores based on regression based norms (age, education, sec, and race) derived from 180 healthy subjects
Sensitivity to MS – Related to Disease Course

Note: Adjusted Z scores based on regression based norms (age, education, sec, and race) derived from 180 healthy subjects.
3 ways to integrate clinically:

- Display on iPad
- Does not require EMR integration
- Direct EMR integration
- Plotting with legacy data
- Enables population of EHR data fields and notes
- Printout
- Does not require EMR integration
- High patient engagement
MSPT-enabled Workflow

1. Patient checks in

2. Medical Assistant:
   - Explains the importance of careful completion of the MSPT assessments
   - Directs patient to the MSPT area
   - Logs the patient in to the MSPT and is available to provide assistance as needed

3. Patient completes MSPT

4. Medical Assistant:
   - Directs patient to the waiting area for routine visit
   - Prints MSPT results report for the care team

5. Care team:
   - Can complete routine visit with access to MSPT results via the MSPT Dashboard, printed results report, or EMR
Legacy workflow

- Activity -
  - Location -
  Lobby -> Hallway -> Exam room -> Office

- Minutes -
  10 5 45 5

- Yield -
  75%
  22%
  No
  No

- Activity -
  - Location -
  Intake space -> Exam room

- Minutes -
  20 45

- Yield -
  90%
  90%
  90%

MSPT-enabled workflow

- Activity -
  - Location -
  PRO MSPT (PRO and PERFO) -> Visit with provider

- Minutes -
  20 45

- Yield -
  90%
  90%
  90%

Provider spends time interpreting data and developing treatment plan with patient, not acquiring and recording data.

= Provider manually acquiring and recording measures in EMR.
How is MSPT transforming clinical research?

The current version of clinical care and research:

CLINICAL CARE

CLINICAL RESEARCH

The future vision of clinical care and research:

CLINICAL CARE

CLINICAL RESEARCH

As supported by the Institute of Medicine, evolving the care model into a continuous learning system can address the spectrum of clinical questions across diverse patient groups generating more evidence for decision making.

Processing Speed Test

Percent of Patients

Z-scores (Age, Sex and Education Adjusted)

Fisher Exact Test, p = 0.0045
Current Status and Future Directions

• Since September, 2015, >7,000 MSPT assessments have been conducted at the Cleveland Clinic in 5,000 unique patients
• Currently installed in 10 MS centers in US and Europe (MS-PATHS Consortium).
• Within the next 2 years, MSPT will be installed in over 100 MS centers worldwide.
## MSPT Teams

<table>
<thead>
<tr>
<th>Development Team</th>
<th>Research Team</th>
<th>Mellen Neurology Team</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jay Alberts</td>
<td>Steve Rao</td>
<td>Rob Bermel</td>
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<tr>
<td>Steve Rao</td>
<td>Malory Weber</td>
<td>Jeffrey Cohen</td>
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<tr>
<td>David Schindler</td>
<td>Christine Reece</td>
<td>Robert Fox</td>
</tr>
<tr>
<td>CCF developers</td>
<td>Jamie Freiberger</td>
<td>Janet Perryman</td>
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<td></td>
<td>Lyla Mourany</td>
<td>Steve Jones</td>
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<td>Genna Losinski</td>
<td>Deb Miller</td>
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<td>Cassie Zimmerman</td>
<td>Amy Fisher</td>
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<td>Jennifer Guadalupe</td>
<td>Jeremy Semmelroth</td>
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<td></td>
<td>Jennie Minnich</td>
<td>Lael Stone</td>
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<td>John Mays</td>
<td>Mary Rensel</td>
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<td></td>
<td>Kaila Parker</td>
<td>Dan Ontaneda</td>
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<td>Dee Ivancic</td>
<td>Alex Rae-Grant</td>
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<td></td>
<td>Suzy Sharp</td>
<td>Devon Conway</td>
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<tr>
<td></td>
<td>Jen Resto</td>
<td>Alissa Willis</td>
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<td>Sneha Natarajan</td>
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<td>Tammy Skaramagas</td>
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<td>Darlene Stough</td>
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<td></td>
<td>Claire Hara-Cleaver</td>
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<td>Marie Namey</td>
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<td>Tangy Kirtz</td>
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<td></td>
<td>Laurel Rubin</td>
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<tr>
<td></td>
<td>Jesse Brillhart</td>
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<tr>
<td></td>
<td>Nataliya Boychuk</td>
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<tr>
<td></td>
<td>Kim Vallejo</td>
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</tr>
</tbody>
</table>
Application to Alzheimer’s Disease
The continuum of Alzheimer’s disease

- Cognitive function
- Preclinical
- MCI
- Aging
- Dementia

Years
Toward defining the preclinical stages of Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease

Reisa A. Sperling[^1], Paul S. Aisen[^2], Laurel A. Beckett[^3], David A. Bennett[^4], Suzanne Craft[^5], Anne M. Fagan[^6], Takeshi Iwatsubo[^7], Clifford R. Jack, Jr.[^8], Jeffrey Kaye[^9], Thomas J. Montine[^10], Denise C. Park[^11], Eric M. Reiman[^12], Christopher C. Rowe[^13], Eric Siemers[^14], Yaakov Stern[^15], Kristine Yaffe[^16], Maria C. Carrillo[^17], Bill Thies[^18], Marcelle Morrison-Bogorad[^19], Molly V. Wagster[^20], Creighton H. Phelps[^21]
Hypothesized Timeframe for Pathophysiological Changes in AD

- Amyloid-β accumulation (CSF/PET)
- Synaptic dysfunction (FDG-PET/MRI)
- Tau-mediated neuronal injury (CSF)
- Brain structure (volumetric MRI)
- Cognition
- Clinical function

Clinical Disease Stage:
- Normal
- Preclinical
- MCI
- Dementia
Model is WRONG When It Comes to Time Scale of Cognitive Deterioration During Preclinical Stage!

Numerous longitudinal studies (Howieson et al., 2008; Edmonds et al., 2015; Jedynak et al., 2012) have reported subtle cognitive deficits in otherwise healthy elders as much as 5 years prior to be diagnosed with MCI/AD. For a review, see Mortamais et al., *Alzheimer’s & Dementia*, 2016, 1-25.
Preclinical Stages in Alzheimer’s Disease

**Stage 1**
Asymptomatic amyloidosis
- High PET amyloid tracer retention
- Low CSF $\beta_{1-42}$

**Stage 2**
Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

**Stage 3**
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

MCI $\rightarrow$ AD dementia
Subtle Cognitive Decline and Biomarker Staging in Preclinical Alzheimer’s Disease

Emily C. Edmondsa, Lisa Delano-Wooda,b, Douglas R. Galaskoa,b,c, David P. Salmonc and Mark W. Bondiа,b,* for the Alzheimer’s Disease Neuroimaging Initiative1

аDepartment of Psychiatry, University of California San Diego, School of Medicine, La Jolla, CA, USA
bVeterans Affairs San Diego Healthcare System, San Diego, CA, USA
cDepartment of Neurosciences, University of California San Diego, School of Medicine, La Jolla, CA, USA

Handling Associate Editor: Jason Brandt
ADNI Biomarkers Used to Operationalize NIA-AA Criteria

Stage 1: Cerebral amyloid accumulation defined by low CSF Aβ$_{1-42}$ level (cutoff < 192 pg/ml)

Stage 2: Neurodegeneration defined by high CSF tau (cutoff > 93 pg/ml) or p-tau$_{181p}$ (cutoff > 23 pg/ml)

Stage 3: Cognitive markers (subtle cognitive decline)
## Neuropsychological Definition of Subtle Cognitive Decline in Preclinical AD

<table>
<thead>
<tr>
<th>Neuropsychological Testing:</th>
<th>Mild Cognitive Impairment</th>
<th>Subtle Cognitive Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired score (&gt;1 SD below age-corrected normative mean) on two measures in the same cognitive domain; or impaired score in each of the three cognitive domains sampled</td>
<td></td>
<td>Impaired score (&gt;1 SD below age-corrected normative mean) on two measures in different cognitive domains</td>
</tr>
</tbody>
</table>

| Functional Abilities: | Functional Assessment Questionnaire score: ≥9 | Functional Assessment Questionnaire score: 6-8 |
Biomarker Prediction of MCI and AD

Total Sample = 570 cognitively normal

- Stage 0 = 24.9% (n = 142)
- Stage 1 = 8.4% (n = 48) amyloid
- Stage 2 = 30.4% (n = 173) tau
- Stage 3 = 8.8% (n = 50) cognition
- SNAP (suspected non-AD pathophysiology, normal amyloid but abnormal neurodegeneration) = 24.2% (n = 138)
- Unclassified = 3.3% (n = 19)
Application of iPad Technology to Alzheimer’s Disease

• AD pathology begins 10-15 years prior to diagnosis.
• Can we detect persons in the preclinical stage of AD?
• Could screen primary care, but widespread PET, MRI, and CSF biomarker testing is impractical due to costs.
• Self-administered computerized cognitive testing, integrated into primary care workflow, could be a low cost and sensitive initial screening method for identifying preclinical AD.
# Cleveland Clinic Computerized Cognitive Battery (C4B)

<table>
<thead>
<tr>
<th>Cognitive Function</th>
<th>Standard NP Measure</th>
<th>C4B</th>
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<tbody>
<tr>
<td>Episodic Memory</td>
<td>Rey Auditory Verbal Learning Test (RAVLT); Brief Visuospatial Memory Test – Revised (BVMT-R)</td>
<td>Visual Memory Test (VMT)</td>
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<tr>
<td>Information Processing Speed</td>
<td>Symbol Digit Modalities Test (SDMT)</td>
<td>Processing Speed Test (PST)</td>
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<tr>
<td>Visual Attention and Task Switching</td>
<td>Trail Making Test (TMT) A &amp; B</td>
<td>Sequencing and Switching Test (SST)</td>
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Cleveland Clinic Computerized Cognitive Battery (C4B)

- 16 minute **self-administered** cognitive battery
- Designed to be similar to standardized measures
- Three cognitive measures:
  - Visual Memory Test (VMT) – episodic learning and delayed memory (similar to BVMT)
  - Processing Speed Test (PST) – information processing speed and incidental learning (similar to SDMT)
  - Sequencing and Switching Test (SST) – visual attention and task switching (similar to Trails A and B)
- All stimuli involve numbers, symbols or letters; auditory instructions easily translated into multiple languages
- Normative database (n = 800, ages 60-89) to be completed by end of 2018
**Visual Memory Test**

Trial 1 of 5

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<td><img src="image" alt="Wrench and Screwdriver" /></td>
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Visual Memory Test

Trial 1 of 5

Done
Processing Speed Test (PST)

Key

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Keyboard

1 2 3 4 5 6 7 8 9
Sequencing and Switching Test (SST)
C4B Advantages

- Like the MSPT, elders being treated in a family/internal medicine clinic would self-administer the 16-minute C4B prior to each visit.
- C4B will be fully integrated into electronic medical records and provide information to guide physicians during clinic visit.
- Declines in cognitive performance derived from repeated C4B assessments can flag individuals at greatest risk for developing AD.
- C4B assesses episodic/incidental memory, information processing speed, visual scanning, and task switching, cognitive domains that are particularly sensitive to changes during the preclinical stage.
- C4B uses nonverbal or number/letter test stimuli, thus allowing the screening battery to be administered in multiple cultures with appropriate translations of the auditory test instructions.
- Cost effective way to test interventions designed to slow or prevent disease progression during the preclinical stage of AD.
Test-Retest Reliability
Test-Retest Reliability

PST

CCC = 0.86

SDMT

CCC = 0.78
Test-Retest Reliability

- SST A
  - CCC = 0.53

- Trails A
  - CCC = 0.63

- SST B
  - CCC = 0.46

- Trails B
  - CCC = 0.71
Convergent Validity

VMT Immediate vs. BVMT Immediate

VMT Delay vs. BVMT Delay

Rho = 0.51

Rho = 0.53
Convergent Validity

PST vs. SDMT

Rho = 0.82
Convergent Validity

SST A vs. Trails A

Rho = 0.53

SST B vs. Trails B

Rho = 0.54
Future Plans

• Integration of C4B into Cleveland Clinic primary care clinics by early 2019

• Submit NIH grant to begin validation studies in 2019:
  
  – PET, MRI, and CSF biomarker testing administered to at-risk primary care patients (ages 60+), who perform 1-2 SD below expectations on cognitive testing adjusted for demographic variables (age, education, sex, race, and ethnicity).
  
  – Patients with other reasons for poor cognitive performance (e.g., history of stroke, trauma, etc.) will be excluded.
Hypotheses

Compared to controls (primary care patients who perform normally on C4B), cognitively at-risk patients will demonstrate:

– greater PET/CSF amyloid and tau burden
– smaller hippocampal volumes
– greater compensatory fMRI activation and lower resting-state functional connectivity in memory regions.
C4B Teams

Development Team
Steve Rao
Jay Alberts
David Schindler
CCF developers

Research Team
Steve Rao
Sara Dubay
Megan Sokolowski
Britt Busson
Christine Reece
Malory Weber

Primary Care/Neurology Team
Lori Posk
James Leverenz
Janet Perryman
Conclusions

• Rather than being the death knell of neuropsychology, I argue that well-designed computerized cognitive measures that allow for screening of large numbers of patients will increase the demand for neuropsychological services.

• Neuropsychologists, due to our expertise in validation of psychometric assessment instruments, should be leading the development of computerized cognitive tests.