

Unmet Needs in Neurodegeneration: Focus on Endpoints

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Disclosures

- Research Support
 - JAI
 - Pfizer
 - Eisai
 - Lilly
 - NIH
 - Alzheimer's Association
- Consultant
 - Athena Diagnostics
- Royalties
 - Psychological Assessment Resources
 - *Neuropsychological Assessment Battery (NAB)*
 - *Boston Qualitative Scores System (BQSS) for the Rey Osterrieth Complex Figure*
 - *Visual Analog Mood Scales (VAMS)*



Outline

- *The ADAS-Cog is History*
- *The Old Stuff just isn't appropriate*
 - *It is likely that clinical trials for MCI or preclinical AD will not succeed simply because of the wrong outcome measures*
- *Patient Report Outcomes may be inappropriate for MCI or early AD Dementia clinical Trials*
- *What is “functional decline” in MCI and early AD Dementia and how can we measure it?*
- *A composite is only as good as the tests that go into it and the sample from which it is derived*

The ADAS-Cog is History

- We are not studying individuals with significant cognitive and functional impairments anymore.
- Even in patients with mild-moderate AD Dementia, the ADAS-Cog was not a great measure.
 - Ceiling effects, skewed distribution
 - *Hobart et al., Alz & Dem 2013; Cano et al., JNNP 2010*
- Just because a measure is accepted by FDA, doesn't mean it should be the "Gold Standard" for every study, for every patient group, forever.

Preclinical AD Staging

Stage 1

Asymptomatic amyloidosis

- High PET amyloid tracer retention
- Low CSF $A\beta_{1-42}$

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 → AD dementia

The Old Stuff Just Isn't Appropriate!

- ADAS-Cog
- MMSE
- CDR
- NTB
- FAQ
- ADCS--ADL
- QoL-AD
- WMS-R Logical Memory
- Etc.



Goal for Appropriate Measure of Episodic Memory

- Highly sensitive to early change.
- Excellent normative data to determine meaningful change and to correct for age, education, gender, and ?ethnicity.
- Minimal floor or ceiling effects.
- NOT a story recall test
 - List learning tests not impacted by executive dysfunction as much and less likely to have practice effects

Goal for Appropriate Measure of Episodic Memory (*cont*)

- Brief administration time
- Equivalent Forms
- Lack of complexity of administration/scoring
- Highly standardized administration and scoring procedures
- Possibility of Computerized administration and scoring
- Multiple Languages with appropriate cultural/linguistic and normative consistency

Goal for Appropriate Measure of Episodic Memory (*cont*)

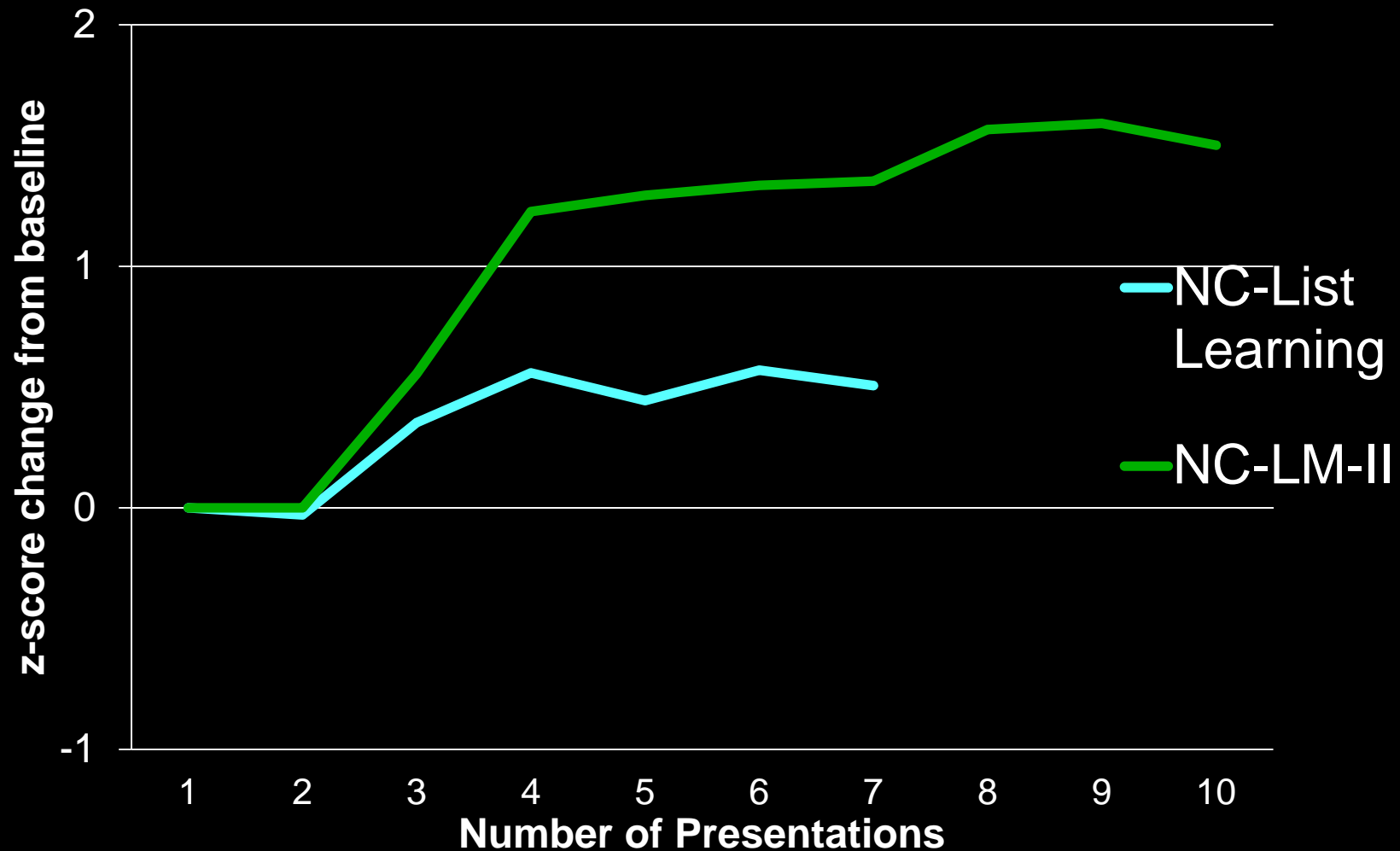
- Excellent psychometric properties
 - Validity
 - It must test what it is supposed to test.
 - Just because a test is called a “memory” test, doesn’t mean it is actually testing the type of memory functioning impacted by hippocampal degeneration.

Goal for Appropriate Measure of Episodic Memory (*cont*)

- Excellent psychometric properties (*cont*)
 - Reliability
 - Test-retest Reliability
 - Alternate-Form Reliability
 - Internal Consistency
 - Limited Practice Effects!

Practice Effects

Comparison between NAB List Learning Delay and WMS-R Logical Memory Delay in Normal Controls over repeated annual administrations at BU ADC



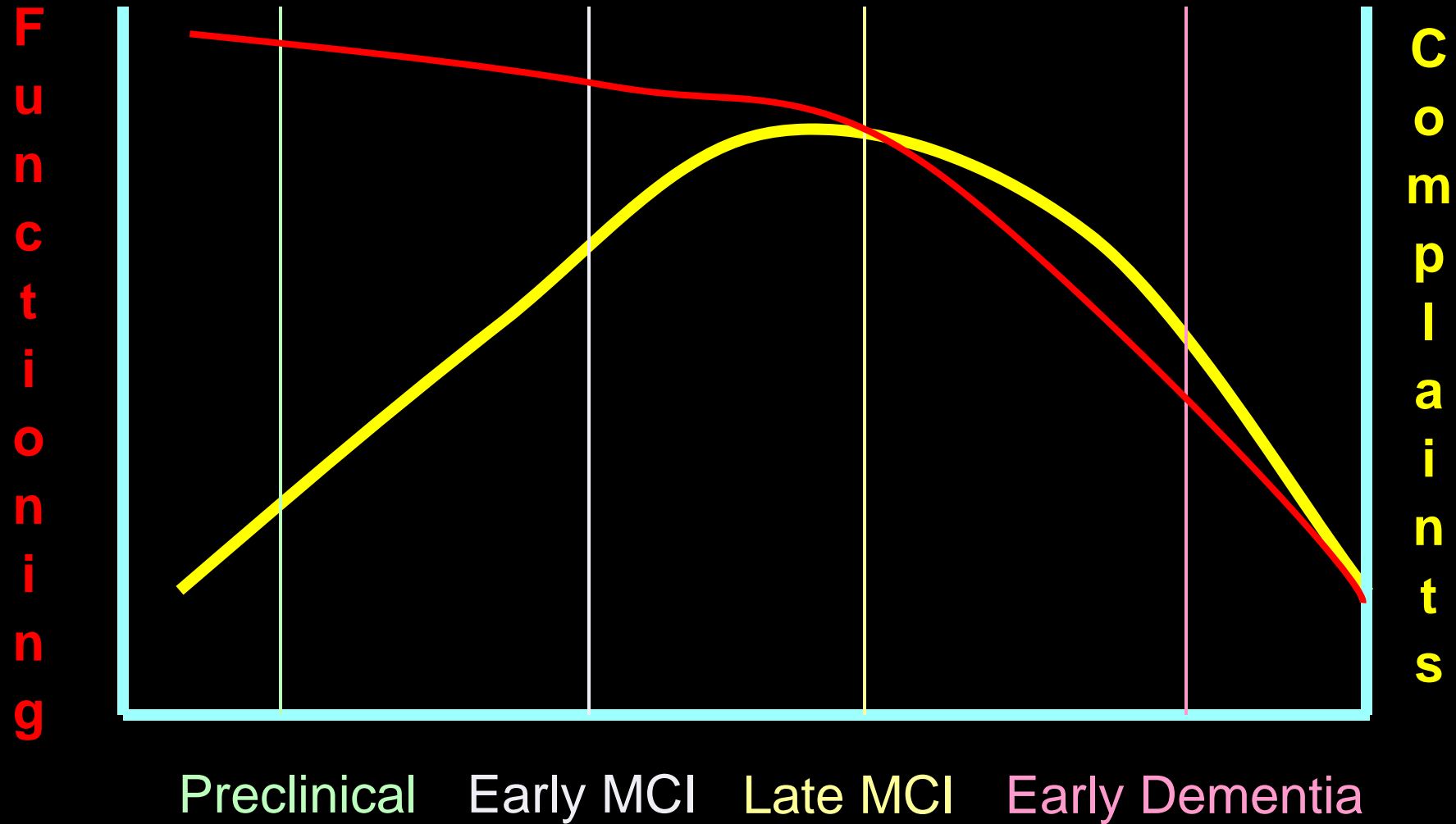
***Patient Report Outcomes may
be inappropriate for MCI or early
AD Dementia clinical Trials***

- Subjective complaint may predate objective change on neuropsychological measures.
- But....

Patient Reported Outcome Measurement *Issues with Self Report of Cognitive Concern*

- Over-reporting in the “worried well.”
 - Cognitive Complaint Index (ADNI)
- Under-reporting due to belief that it is “normal” to have cognitive impairments or “senior moments.”
- Biggest Issue: As underlying disease worsens, so does the growing lack of awareness of having any problems due to “**anosognosia.**”
 - the neurologically based inability to be aware that one has a neurological problem

The Anosognosia Problem



Abnormal

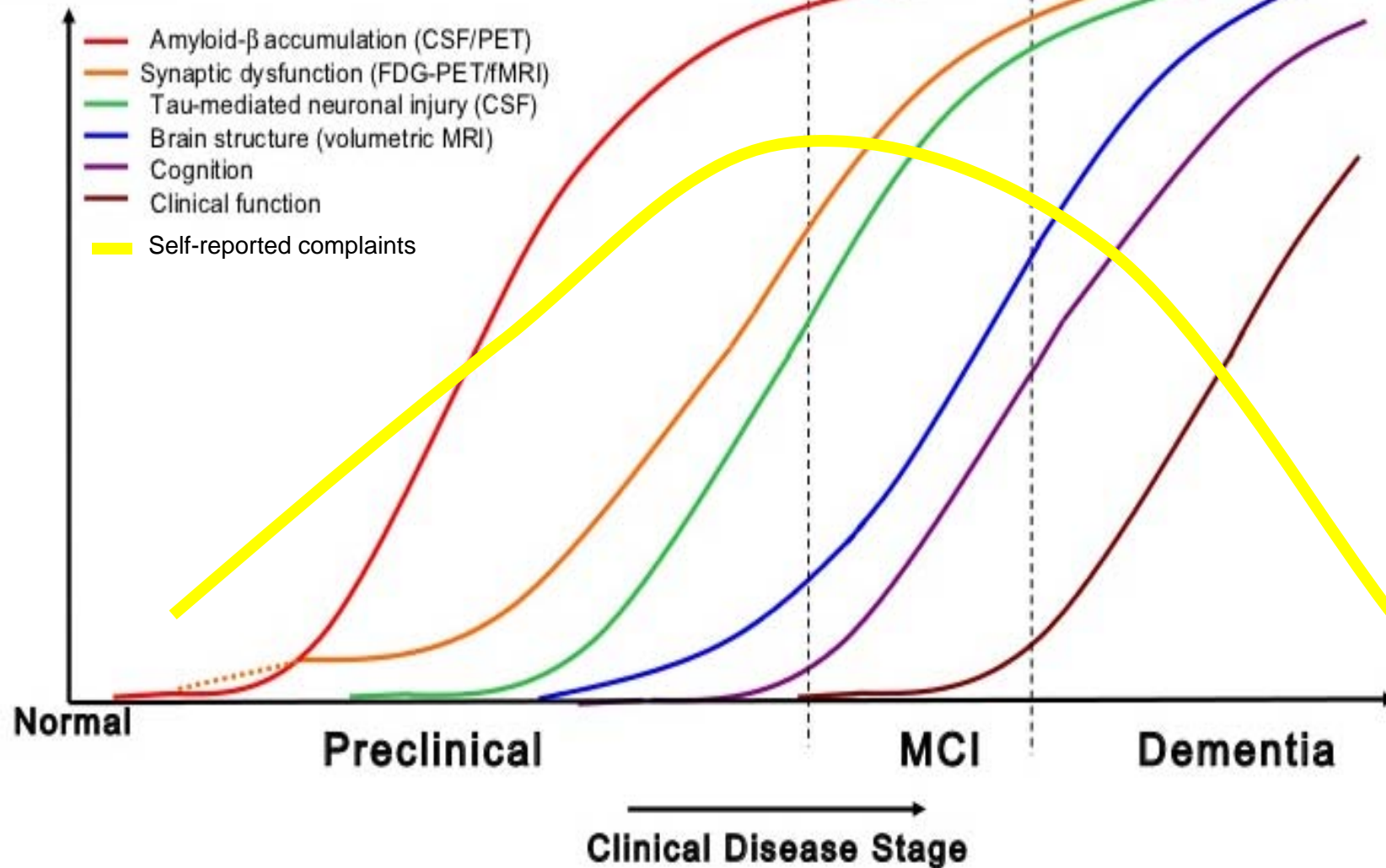


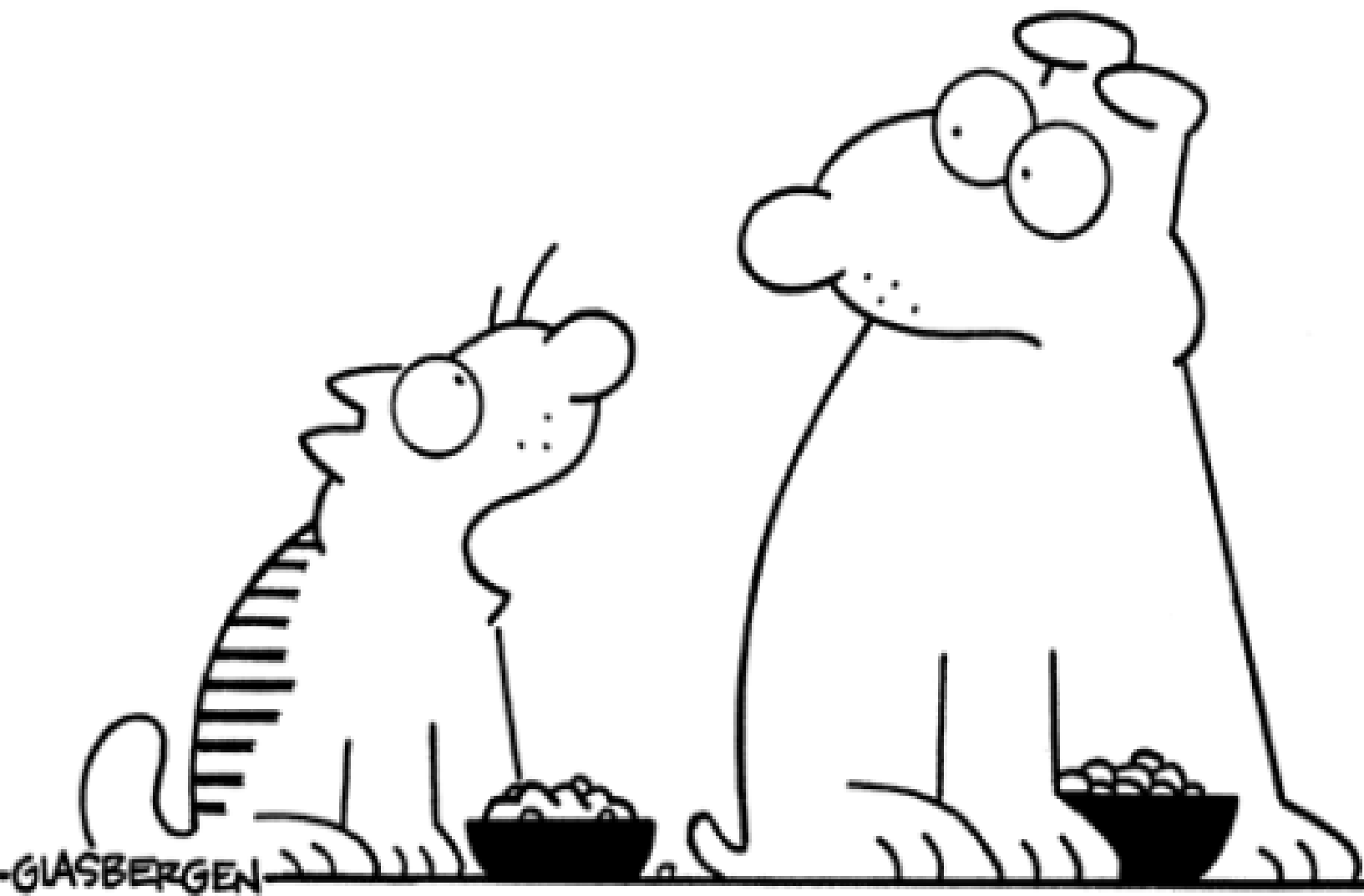
Figure adapted from Jack *et al.* 2010
Sperling *et al* *Alzheimer & Dementia* 2011

Issues with Informant Report of Cognitive Concern

- No informant available for prevention studies
- Poor informant (lack of contact, impaired, etc.)
- Secondary gain or other reasons to diminish or exaggerate problems
 - Marital or family discord
 - Denial
 - Afraid of confrontation or decreasing independence

What is “functional decline” in MCI and early AD Dementia?

- What is the threshold for considering something as having an impact on independence?
 - “Mild”.... “Significant”
- What aspect of life? – Work, Housework, Finances, Hobbies?
- What are “instrumental activities of living?”
 - Using a telephone, paying taxes, cooking, driving, using a computer
- Once again, there may be a difference between self- and informant-report
- There may be a difference between someone with lots of responsibility and daily challenges versus someone who stays at home without responsibility.



“The vet says i need a hobby. I thought eating and sleeping were my hobbies!”

Performance-Based Measures of Daily Functioning



Performance-Based Measures of Daily Functioning

- Not meant to replace an appropriate measure of “actual” functioning.
- Objective measurement
- Face validity
- Ecological validity
- Examples from Neuropsychological Assessment Battery (NAB)







Edison Electric Company

Statement

Harold Evanston
3409 Chestnut Road, Apt. #64
Greenacres, MD 20976

Account Number: 661-837-1842 002

Bill Period: January 16 - February 16

Account Summary:

	<i>Amount</i>	<i>Total</i>
Previous Balance	\$60.83	
Payment Received (1/23)	\$60.83	
Balance as of January 23	\$0	
New Charges	\$67.29	
Total Amount Due		\$67.29

Date of Statement	Payment Due Date	Total Amount Due
February 16	March 2	\$67.29

Payment Instructions:

*Please make check payable to **Edison Electric Company**.*

Please include your account number on the check. Send payment to: Edison Electric Company, 4000 Medway Street, Dennis, MD 21986-4600.

Check No.	Date	Transaction Description	Subtraction	Addition	Balance
1098	1/21	1-900-Bouquet	\$17.42		\$113.99
1099	1/28	Nick's Barber Shop	\$24.73		\$89.26
1100	2/7	Nippon Restaurant	\$46.29		\$42.97
	2/8	Deposit		\$350.00	\$392.97
1101	2/11	Sleepy Mattresses	\$275.68		\$117.29
1102	2/16	Maryland Municipal Court	\$40.00		\$77.29

<p>Harold Evanston 3409 Chestnut Road, Apt. #54 Greenstown, MD 20976</p>	<p>No. 1103</p>
	<p>Date: <u>February 23</u></p>
<p>Pay to the Order of _____</p>	<p>\$ <input type="text"/></p>
	<p>_____ Dollars</p>
<p>Memo: _____</p>	<p><u>Harold Evanston</u></p>

- Take one yellow pill two times a day with food.
- Take two green capsules before bed.

First Medication Instruction

- Take one green pill twice a day with food.
- Take one yellow capsule two times a day with food.
- Take one yellow pill two times a day with food.
- Take two yellow pills two times a day with food.

Second Medication Instruction

- Take two green pills before bed.
- Take two green capsules before bed.
- Take two yellow capsules before bed.
- Take one green capsule before bed.

Diana Rivera

31 Stedman Court

Pottersville

474-2569

First Name

Julie

Rebecca

Diana

Delores

Last Name

Riley

Davies

Garcia

Rivera

Street Number

38

91

13

31

Street Name

Summit

Stedman

Caswell

Maple

Street Ending

Court

Way

Trail

Lane

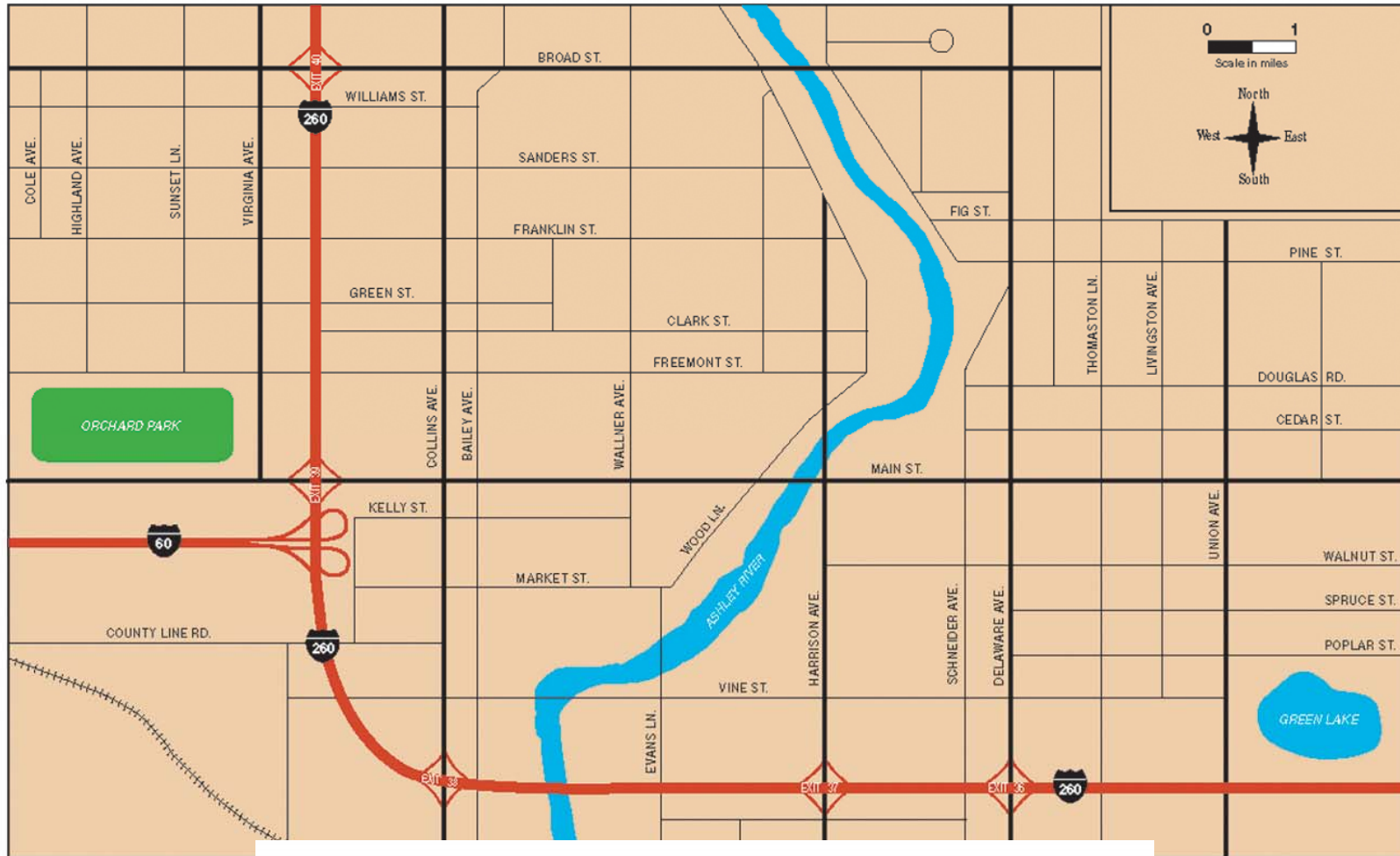
Town

Hopeville

Powell

Pottersville

Grovedale



On Highway 60, travel east. What would your location be if you entered Highway 260 heading south, got off at the third exit, and traveled 2 miles north?



2. Judgment

Recording	Scoring	Discontinuation
Record responses verbatim. If examinee is queried to say more, place a Q in brackets [Q] at that point in examinee's response.	See criteria on page 7.	Administer entire task.

Administration Instructions

Say, **I am going to ask you a few questions. I want you to answer each question as fully as possible.** Questions may be repeated up to three times at examinee's request. If response is very brief or includes only a general concept (e.g., "For safety," "For health," or "It's dangerous") with no specific reference to the question, query by saying, **Tell me more.**

Question	Response
1. Why should you blow out candles before going to bed?	
2. Why should you not leave a young child alone at home?	
3. Why should you replace the batteries in a smoke detector regularly?	
4. What should you do if you take too much of a prescription medication?	
5. Why should you not unplug electrical appliances while your hands are wet?	
6. Why are certain foods marked with an expiration date?	
7. Why is it important for people to brush their teeth?	
8. Why is it important to tell your doctor all the medications that you are taking?	
9. Why should you wash your hands before eating?	
10. What does it mean when your doctor says that there is a 25% chance of having serious side effects from a treatment?	

Go to page 8 →

Questions With Scoring Criteria	Score
<p>1. Why should you blow out candles before going to bed? 2 points: Addressee potential danger of fire 1 point: No 1-point responses for this question 0 points: Inaccurate or vague</p>	2 0
<p>2. Why should you not leave a young child alone at home? 2 points: Addressee children not able to care for themselves or dangers of being left alone (2 or more examples) 1 point: Addressee general danger to child or home or 1 example of potential danger if child left alone 0 points: No acknowledgment of possible danger to child or that child is unable to care for himself/herself</p>	2 1 0
<p>3. Why should you replace the batteries in a smoke detector regularly? 2 points: Addressee dangerous consequences of inoperable smoke detector 1 point: Smoke detector needs batteries to operate 0 points: Inaccurate or vague</p>	2 1 0
<p>4. What should you do if you take too much of a prescription medication? 2 points: Addressee need for <u>immediate</u> response (i.e., calling 911, Poison Control) 1 point: Addressee at least 1 appropriate immediate response BUT includes 1 inappropriate response 0 points: No mention of appropriate immediate response; "induce vomiting" is an inappropriate response</p>	2 1 0
<p>5. Why should you not unplug electrical appliances while your hands are wet? 2 points: Addressee potential danger of shock/electrocution AND concept of water acting as a conductor of electricity 1 point: Addressee potential danger of shock/electrocution BUT not concept of water acting as a conductor of electricity 0 points: Does not address potential danger of shock/electrocution or concept of water acting as a conductor of electricity</p>	2 1 0
<p>6. Why are certain foods marked with an expiration date? 2 points: Addressee potential for food spoilage after date AND potential for sickness after eating the food 1 point: Addressee food spoilage after date BUT no mention of becoming sick 0 points: No indication of food spoilage or food being rotten</p>	2 1 0
<p>7. Why is it important for people to brush their teeth? 2 points: Addressee 2 or more specific reasons to brush, with at least 1 reason addressing health aspects 1 point: Addressee only 1 specific reason to brush for health of teeth/gums or vaguely addresses oral hygiene 0 points: No mention of teeth/gum health OR only very vague allusion to health</p>	2 1 0
<p>8. Why is it important to tell your doctor all the medications that you are taking? 2 points: Addressee potential danger of interaction, contraindications, or side effects 1 point: Addressee doctor's knowledge and/or doctor's need to know everything about medical status 0 points: Addressee unrelated medical issue or fails to address danger in any way</p>	2 1 0
<p>9. Why should you wash your hands before eating? 2 points: Addressee <u>spread</u> of germs/bacteria from hands to food/mouth 1 point: Addressee germs/bacteria but not the spread to food/mouth 0 points: No mention of germs, bacteria, infection, or health aspects</p>	2 1 0
<p>10. What does it mean when your doctor says that there is a 25% chance of having serious side effects from a treatment? 2 points: Addressee understanding of 1 in 4, 1/4 of people, 25 in a 100 chance of having side effects or 75% chance of not having side effects 1 point: General statement that treatment could cause problem OR rewording side effects issue without rewording percentage risk issue OR addressee results of previous clinical trials without the issue of risk 0 points: Response lacks appropriate understanding of percentage risk OR just repeats the original wording</p>	2 1 0
Judgment (JDG) Raw Score	

1. Why should you blow out candles before going to bed?		6. Why are certain foods marked with an expiration date?	
2. Why should you not leave a young child alone at home?		7. Why is it important for people to brush their teeth?	
3. Why should you replace the batteries in a smoke detector regularly?		8. Why is it important to tell your doctor all the medications that you are taking?	
4. What should you do if you take too much of a prescription medication?		9. Why should you wash your hands before eating?	
5. Why should you not unplug electrical appliances while your hands are wet?		10. What does it mean when your doctor says that there is a 25% chance of having serious side effects from a treatment?	

Composites

- Believed to be an improvement over use of individual tests as primary outcome measures, especially for adaptive trials
- **Goals:**
 - Smaller samples, Greater power, Shorter studies
- **Reality:**
 - Typically derived from NP measures (as well as ADL and CDR) used in MCI/AD samples
 - May not be appropriate for early MCI or Preclinical samples if developed on later stages
 - Composite scores are only as good as the individual NP measures they are derived from

New Composite Study - CTAD 2013

Ropacki, Hendrix, Seichepine & Stern

- Measures with good psychometric properties and from early MCI yielded improved Composite
 - Outperformed Composites based on older measures used in AD Clinical Trials to-date
- Overall MSDR of 0.71 for the Composite
 - Higher than observed for the Composite of ADAS-Cog, MMSE and NTB items in a pooled ADCS & ADNI MCI population of 0.48
 - Higher than observed for best Composite of ADAS-Cog, MMSE and CDR-SB items of 0.54

Summary

- The old measures of cognition and daily functioning used in AD Dementia clinical trials are not appropriate for prodromal, early MCI, and early dementia trials.
- Patient report outcomes sound good in theory, but....
- Performance-based measures of daily functioning may be helpful.
- Composites are great, but...

