Developing More Effective Paradigms for Assessing and Monitoring Memory and Cognitive Change Across the MCI and PreMCI Spectrum

David A. Loewenstein, PhD

University of Miami School of Medicine

What is the Importance of Good Cognitive and Functional Assessment In Clinical Trials?

- Recent guidelines forwarded by the FDA suggest they will not consider the approval of a medication using a biomarker as a surrogate outcome measure in AD (*at any stage of the illness*) until there is widespread evidence-based agreement that an effect on a particular biomarker is reasonably likely to predict *clinical benefit*.
- Such benefit will most likely need to be identified and measured as individuals transition from normal to Pre-MCI or MCI states

Loewenstein and Duara eta al (2012) An Investigation of PreMCI: Subtypes and Longitudinal Outcomes *Alzheimer's Dementia*

Groups	Subjects	Progression to MCI or Dementia (2-3 Years)
Normals	N=162	3.7%
PreMCI Clinical Only	N=41	22.0%
PreMCI Mild Memory Imp- **Clinically Normal**	N=48	16.7%
PreMCI Mild Memory Imp- **Clinically Normal**	N=18	38.9%

Can we construct a Cognitive Stress Test To Measure Subtle Cognitive Dysfunction ?

One Model: Vulnerability to Semantic Interference as an Early Marker of Alzheimer's Disease

SEMANTIC INTERFERENCE TEST (SIT)
(Loewenstein, Acevedo and Duara et al, 2004)

- Ten common objects are presented and recalled over three learning trials
- Introduce 10 additional objects for recall which are **semantically** related to items on 1st list (e.g., fork for spoon; comb for brush)
- **Proactive Interference-** Old learning interferes with new List B learning
- **Retroactive Interference-** New List B Learning interferes with recall of original targets

Interference Effects In Learning and Memory

- Proactive Interference- Old Learning Interferes with New Learning

- Retroactive Interference- New Learning Interferes with Old Learning

- We are not dealing with any type of interference, we are dealing with :

SEMANTIC INTERFERENCE

Sensitivity and Specificity of the SIT in the early Detection of MCI-AD

MCI-AD Sensitivity= 84.6%

Normal Elderly Specificity= 96.2%

SIT Longitudinal Findings

(Loewenstein, D.A., Acevedo, A., Agron, J. & Duara, R. Dementia and Geriatric Cognitive Disorders, 2007)

- **Relative to a wide array of neuropsychological measures List B recall (susceptible to proactive interference) was more highly predictive of decline from MCI to dementia over an average 30 month period than standard memory tests such as Memory for Passages and Visual Reproduction**

Association Between Florbetapir SUVR, SIT and Different Memory Measures in 17 Nondemented Community Dwelling Persons with Memory Complaints

	SUVR Total	Anterior Cingulate	Posterior Cingulate
Fuld Object Memory Evaluation	r= -.08	r= -.16	r= -.25
Delayed Logical Memory For Passages	r=-.48	**r=-.57***	**r=--.57***
SIT List B (subject to proactive interference)	**r=-.64 ****	**r=-.72 ****	**r=-.66 ***
Short-Delay List A Cued Recall (subject to retroactive interference)	r=--.43	r=-. 49	**r=-. 69****

What are some limitations of widely used cognitive measures?

1) They are susceptible to attention and salience at acquisition (e.g., Memory for a Story Passage)
2) Persons have individualized strategies for learning (those with high cognitive reserve can do much better)
3) Many cognitive tests are are not orthogonal and measure many different cognitive functions
4) Individuals are compared to group means instead of comparing elements of their own performance
5) Neuropsychological measures can be noisy and prone to practice effects

More Advanced Semantic Interference Paradigms

- Loewenstein-Acevedo Scales for Semantic Interference and Learning (LASSI-L)

An Evaluation of Deficits in Semantic Cueing and Proactive and Retroactive Interference as Early Features of Alzheimer's Disease

Elizabeth Crocco, M.D., Rosie E. Curiel, Psy.D., Amarilis Acevedo, Ph.D., Sara J. Czaja, Ph.D., David A. Loewenstein, Ph.D.

Objectives: *To determine the degree to which susceptibility to different types of semantic interference may reflect the initial manifestations of early Alzheimer disease (AD) beyond the effects of global memory impairment.* **Methods:** *Normal elderly (NE) subjects (n = 47), subjects with amnestic mild cognitive impairment (aMCI; n = 34), and subjects with probable AD (n = 40) were evaluated by using a unique cued recall paradigm that allowed for evaluation of both proactive and retroactive interference effects while controlling for global memory impairment (i.e., Loewenstein-Acevedo Scales of Semantic Interference and Learning [LASSI-L] procedure).* **Results:** *Controlling for overall memory impairment, aMCI subjects had much greater proactive and retroactive interference effects than NE subjects. LASSI-L indices of learning by using cued recall revealed high levels of sensitivity and specificity, with an overall correct classification rate of 90%. These measures provided better discrimination than traditional neuropsychological measures of memory function.* **Conclusions:** *The LASSI-L paradigm is unique and unlike other assessments of memory in that items posed for cued recall are explicitly presented, and semantic interference and cueing effects can be assessed while controlling for initial level of memory impairment. This is a powerful procedure that allows the participant to serve as his or her own control. The high levels of discrimination between subjects with aMCI and normal cognition that exceeded traditional neuropsychological measures makes the LASSI-L worthy of further research in the detection of early AD.* (Am J Geriatr Psychiatry 2013; ■:■—■)

Key Words: early Alzheimer's, early detection, MCI, memory, proactive interference, semantic interference, semantic cueing

PRESENT *LIST A* TARGET WORDS BELONGING TO THREE SEMANTIC CATEGORIES:

Fruits	Clothing	Musical Instruments

Cued Recall of ***List A*** Targets

Present ***List A*** Targets Again

Second Cued Recall of ***List A*** Targets

Cued Recall of ***List B*** Targets
(Most Susceptible to Proactive Interference)

Present ***List B*** Targets Again

Second Cued Recall of ***List B***

DELAYED Cued Recall for ***List A*** Targets
(*Most Susceptible to Retroactive Interference*)

LASSI-L Administration Instructions:

Examiner: *"You will see 15 words, one at a time. The words will be **fruits**, **musical instruments**, or **articles of clothing**. Each time I show you a word, I want you to read it out loud.*

*Later on, I am going to ask you to tell me, from memory, all of these words, which will be **fruits**, **musical instruments** or **articles of clothing**. Read each word out loud so that you can remember it later."*

The Subject Needs to Use Cued Recall Over Two Trials to **Maximize Storage** of the Fifteen Targets

A second List of 15 Targets are presented belonging to same semantic categories

Cued recall and recognition for List 2 targets are subject to **Proactive Interference**

Cued recall and recognition for List 1 targets are subject to **Retroactive interference**

20-Minute Delayed Cued Recall and Recognition

LASSI-L Findings
(Crocco et al., 2013, AJGP; Curiel et al, 2013;JAS)

- LASSI-L subscales all have extremely high test-retest reliabities
- Strongest Predictors in Logistic Regression and R0C Models is List A2 Cued Recall and List B1 Cued Recall (Sensitivity and specificity for MCI versus normal subjects is 87.9%/91.5%)

Association Between Medial Temporal Atrophy and LASSI-L Measures in 16 MCI Patients

	MTA Left	MTA Right
List A1 Cued Recall	r= -.43	r= -.40
List A2 Cued Recall	**r=-.53***	**r=-.57***
List B Cued Recall	**r=-.75*****	**r=-.58***
Short-Delay A Cued Recall	r=-. 04	r=-. 14

Association Between Florbetapir SUVR and LASSI-L Measures in 17 Nondemented Subjects with Memory Complaints

	SUVR Total
List A1 Cued Recall	r= -.44
List A2 Cued Recall	r=-.38
List B1 Cued Recall	r=-.15
List B2 Cued Recall	**r=-. 56***
Short Delay Cued Recall	r=-.10

Association Between SUVR and LASSI-L Measures in 17 Nondemented Subjects with Memory Complaints

	Precuneus	Posterior Cingulate	Frontal	AC	Temporal
List A1 Cued Recall	**r= -.60 ****	**r= -.74****	r=-.50	r= -.46	r=-. 48
List B2 Cued Recall	**r= -.62 ***	**r=-. 66****	r=-.45	r=-. 14	**r=-.54***

Computerized LASSI-L

- Cued recall and associative paradigms allows for computer generated administration with all the benefits of portability and reliable delivery in clinical trials

Harmonica	Spoon	Horse	Lighter	Train

Touch the word that is an animal

Harmonica

Spoon

Horse

Lighter

Train

Harmonica	Spoon	Horse	Lighter	Train

Touch the word that is a musical instrument

Harmonica

Spoon

Horse

Lighter

Train

You will see a set of 4 pictures

Touch the picture that corresponds to the word that you saw previously

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What Advantages Are Provided by the LASSI-L and Similar Paradigms

- Controlled learning to minimize variability in learning strategies
- Maximize Storage and Consolidation of to-be-remembered material
- Elements of performance (i.e., susceptibility to proactive and retroactive interference can be compared to each other)
- Elements such as maximum recall should be sensitive progression as an individual progresses towards dementia
- Easily amenable to computerized testing to allow for ease of administration, lack of experienced psychometrist and portability for clinical trials or remote assessment

THANKS TO MEMBERS OF OUR TEAM!

University of Miami

Sara Czaja, PhD

Philip Harvey, PhD

David Loewenstein, PhD

Rosie Curiel, PsyD

Elizabeth Crocco, MD

Samir Sabbag, MD

Sankarin Nair, MS

Clinton Wright, MD

Mount Sinai (Miami Beach)

Ranjan Duara, MD

David Loewenstein, PhD

Daniel Varon, MD

Warren Barker MS

Maria Greig-Custo, MD