
The Development of Novel Cognitive Stress Paradigms for Detection of Early Cognitive Impairment in Cross-Cultural Research.

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EARLY DETECTION OF ABNORMAL MEMORY PROCESSES

- By the time a person has been diagnosed with dementia of the Alzheimer's type, significant deterioration has occurred in many areas of the brain.
- Detection of the earliest stages of Alzheimer's disease can enable innovative new therapies that can be initiated before significant brain degeneration has occurred.



MCI and Pre-MCI

- Early in the course of Alzheimer's disease, a person can be diagnosed with mild cognitive impairment (MCI) which does not greatly affect a person's everyday activities of daily living.
- Loewenstein et al (2012) has found that an even earlier cognitive state can be identified in which the person is not cognitively normal but does not meet formal criteria for **MCI**
- Some individuals may have memory complaints corroborated by an informant and completely WNL on standard cognitive testing (**PreMCI-Clinical**)
- Other individuals but have memory and other deficits on formal cognitive testing but no history of memory complaints after careful clinical interview with an older adult and family members (**PreMCI-Cognitive**)



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

Groups	Subjects	Progression to MCI or Dementia (2-3 Years)
Normal Cognition	N=162	3.7%
PreMCI Clinically Impaired, No Neuropsychological Impairment	N=41	22.0%
PreMCI Clinically Normal, Mild Memory Imp (1 test)	N=48	16.7%
PreMCI Clinically Normal, Mild Memory Imp (2 tests)	N=18	38.9%

CURRENT NEUROPSYCHOLOGICAL MEASURES

- The vast majority of neuropsychological measures are based on cognitive paradigms six or seven decades old.
- Concern that current measures may not capture the earliest stages of early Alzheimer's Disease
- Can we develop cognitive stress paradigms analogous to exercise EKGs?



New Semantic Interference Paradigm

- Loewenstein-Acevedo Scales for Semantic Interference and Learning (LASSI-L)
- Controlled learning (category cues are given at both the acquisition and retrieval stages of learning)
- This promotes optimal learning of to-be-remembered targets, minimizes individual differences in learning.
- Sets the stage for optimal tests of proactive and retroactive semantic interference effects
- The LASSI-L is the only memory paradigm to assess recovery from proactive interference effects



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

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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 amnesic 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,

LASSI-L Findings

(Crocco et al., 2013, AJGP; Curiel et al, 2013;JAS)

Sensitivity and Specificity of the LASSI-L in the
early Detection of MCI-AD

MCI-AD Sensitivity= 87.9 %

Normal Elderly Specificity= 91.5 %



15 *List A* Target Words, Three Semantic Categories:

Fruits

Clothing
Instruments

Musical

Cued Recall of *List A* Targets

After Presentation, Second Cued Recall of *List A* Targets

Present *List B* Targets

First Cued Recall of List B (Proactive Interference)

Present *List B* Targets Again

Second Cued Recall of *List B* (Recovery from Proactive Interference)

Cued Recall List A (Retroactive Interference)

Loewenstein et al (2016) American Journal of Geriatric Psychiatry

PARTICIPANT GROUPS *(No person could have Impaired IADLs)*

- **Normal Cognition-** Clinician Dx and Neuropsychological (NP) Tests are WNL: No Memory Complaints
- **Subjective Cognitive Impairment-** Memory Complaints but Clinical and NP Exam Normal
- **aMCI-** Memory Complaints and both the Clinical and NP Exam indicate MCI
- **PreMCI-** The Clinical Dx indicates that the patient shows evidence for and history of cognitive impairment but the NP is normal



LASSI-L was not used in diagnostic formulations leading to assignment into a specific diagnostic group.



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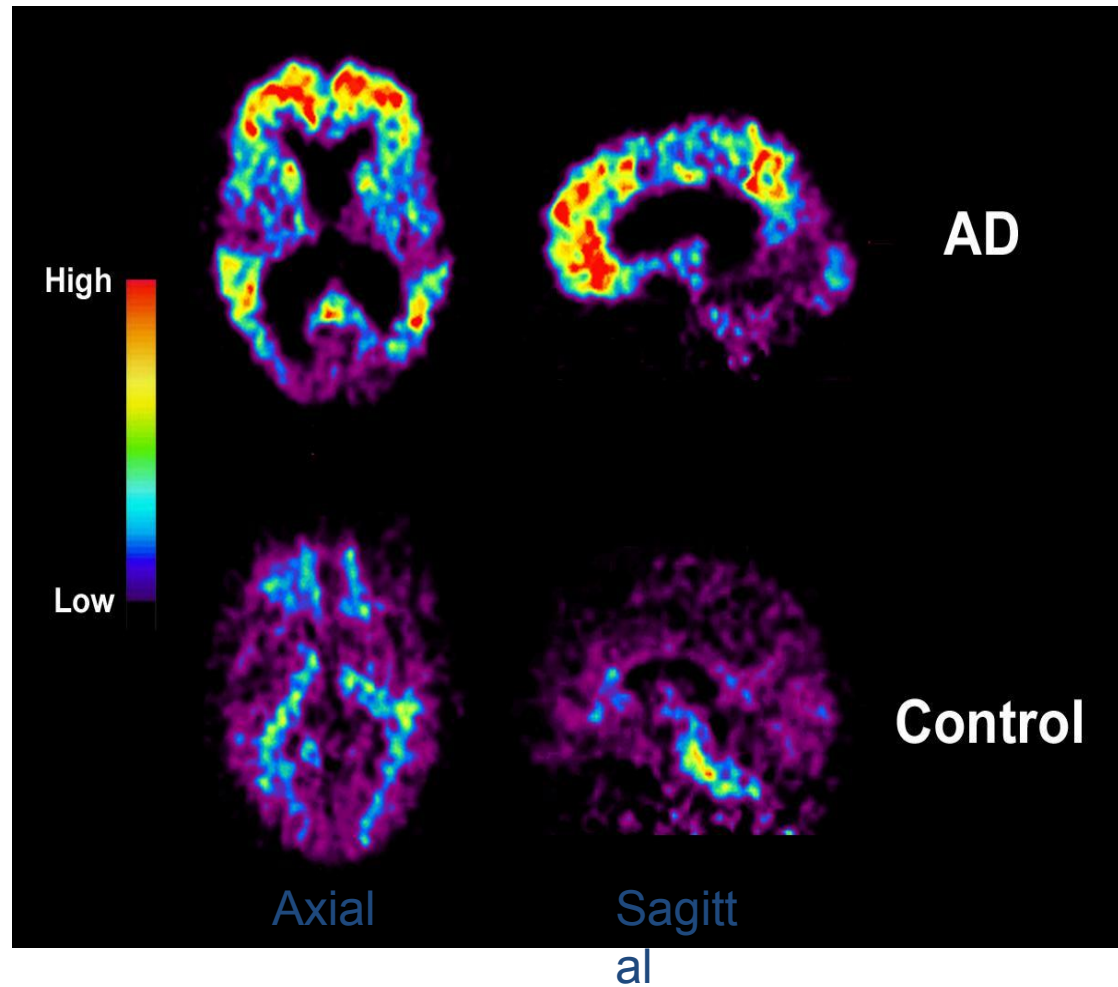
Demographic Information for Different Participant Groups

	Cognitively Normal (n=31)	Subjective Memory Disorder (n=18)	PreMCI Clinical (N=15)	Amnestic MCI (n=29)	F or χ^2 Value
Age	72.6 (7.8)	76.9 (6.7)	77.5 (7.5)	78.2 (6.2)	F=3.2*
Education	16.2 (2.7)	14.5 (3.0)	15.6 (3.3)	14.2 (2.7)	F= 2.1
Gender (Female)	74.1%	87.5%	54.5%	61.5%	$\chi^2=4.4$
MMSE Scores	29.3 ^a (.7)	28.8 ^a (1.1)	29.1 ^a (.9)	26.9 ^b (2.0)	F=16.2***

IMPAIRED PERFORMANCE OF 93 COMMUNITY PARTICIPANTS WITH DIFFERENT CLIED

	LASSI-L A-2 ≤ 10 $\chi^2=15.7$ ***	LASSI-L B-1 ≤ 4 $\chi^2=27.7$ ***	LASSI-L B-2 ≤ 8 $\chi^2=30.9$ ***	Any LASSI-L Deficit $\chi^2= 37.8$ ***
Normal Cognition (n=31)	0%	12.9%	0%	12.9%
Subjective Memory Complaints (n=18)	5.6%	33.3%	16.7%	38.9%
PreMCI Clinical (N=15)	0%	46.7%	26.7%	46.7%
a-MCI (n=29)	31.1%	78.6%	60.7%	89.3%

[¹¹C] PIB and PET: In Vivo Imaging of β -Amyloid Plaques



PIB = Pittsburgh compound-B; PET = positron emission tomography. Image courtesy of William E. Klunk, MD, PhD, and Chet Mathis, PhD.
—Source: Klunk WE et al. *Ann Neurol*. 2004;55:306-319.

Association Between SUVR and LASSI-L Measures in 23 Subjects without MCI or Neuropsychological impairment

	Total SUVR	Anterior Cingulate	Posterior Cingulate	Precuneus	Frontal
List A1 Cued	r=-.44*	r= -.49 **	r=-.35	r=-.47*	r= -.44 **
List A2 Cued	r=-.26	r=-.31	r=-.19	r=-.32	r=-.20
List B1 Cued	r=-.44*	r=- .42*	r=-.41 *	r= .40	r=-.31
List B2 Cued Recall	r=-.60 **	r= -.48 **	r=-.50**	r= -62**	r= -.43 *
Delayed Passages	r=-. 29	r=-.15	r=-. 08	r=-.20	r=-.36*

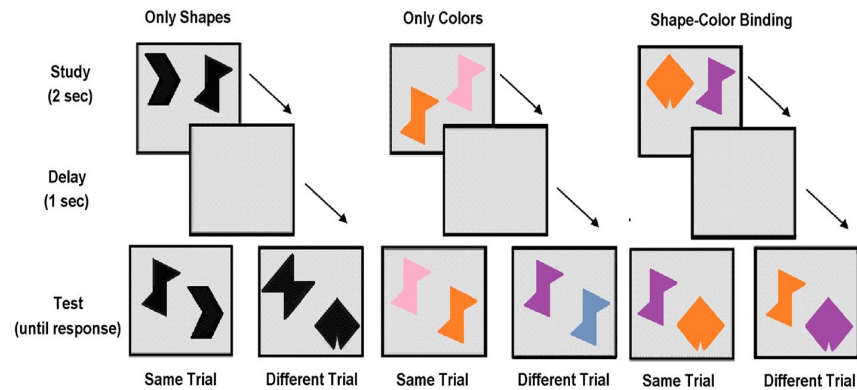
Demographic Information for Different Participant Groups IN MRI-LASSI-L STUDY (Loewenstein, Curiel et al, Journal of Alzheimer's Disease.2017)

	Cognitively Normal (n=37)	MCI (n=32)	F or X ² Value
Age	74.2 (SD=7.8)	74.8 (SD=8.2)	.12
Education	14.6 (SD=3.6)	14.9 (SD=3.5)	.09
Gender (Female)	67.6 % female	53.1 % female	.96
MMSE Scores	28.7 (SD=1.6)	27.0 (SD=2.3)	12.22***

Association Between MRI Reductions and Memory Impairment in 32 MCI PARTICIPANTS

	Hippocampus	Precuneus	Superior Parietal	Temporal Pole	Inferior Lateral Ventricle
List A2 Cued	r=-.48**	r= .15	r=-.30	r=-.30	r= -.44*
List B1Cued	r=-.36*	r=-.34	r=-.38	r=-.20	r=-.36*
List B2 Cued	r=- .49**	r=- .54 ***	r=- .49**	r= .49**	r=-.51**
HVLT-R Delayed Recall	r=-.09	r= -.10	r=.01	r= -.01	r= -.07
NACC Delayed Passage	r=-.14	r=-.02	r=-.04	r=-.04	r=-.10

Visual Memory Binding Test



Comparison of 105 Elderly Participants aMCI (n=49) and Cognitively Normal (n=56) Elderly on LASSI-L and VMBT

	Area under ROC Curve	Sensitivity	Specificity
LASSI- Cued A2 (Maximum Storage)	.842 (SE=.04)	73.5%	80.0%
LASSI- B1 Cued Recall (Vulnerability to pSI)	.747 (SE=.05)	67.3%	78.6%
LASSI- B1 Cued Recall (Lack of Recovery from pSI)	.836 (SE=.04)	75.5%	76.8%
Visual Memory Binding Test % Shapes	.730 (SE=.05)	57.1%	69.6%
Visual Memory Binding Test % Color/Shapes	.678 (SE=.05)	51.1%	71.4%

Logistic Regression- Predictors of Diagnosis of aMCI and Cognitively Normal Elders

Entered	Sensitivity	Specificity	Overall
Cued B2	75.5%	76.8%	76.2%
Cued B2 Cued A2	73.5%	85.7%	80.0%
Cued B2 Cued A2 %Shapes	75.5%	87.5%	81.9%



SUMMARY AND CONCLUSIONS

- The LASSI-L distinguishes between PreMCI, aMCI and Normal participants
- Failure to recover from proactive interference is most associated with amyloid load in multiple brain regions among non-MCI and non-demented community-dwelling subjects
- LASSI-L measures, particularly failure to recover from PSI are more highly related to amyloid load than other cognitive measures
- The LASSI-L uses controlled learning, cued retrieval and is more educationally and culturally fair



Potential Importance of this Work

- What is normal versus abnormal memory, other cognitive and functional decline
- Can newly developed measures detect the earliest changes going on in the brain and the central nervous system
- Can early detection lead to earlier, more effective interventions?
- How do we apply the LASSI-L in different cross-cultural groups...





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