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# **Detection of the Very Earliest Stages of Alzheimer's Disease Using Cognitive Testing and Brain Imaging**

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# CURRENT NEUROPSYCHOLOGICAL MEASURES

- The vast majority of neuropsychological measures are based on cognitive paradigms six or seven decades old
- There is 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?**



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# LASSI-L Cognitive Stress Test



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

- **Controlled learning** of 15 words 3 categories (animals, fruits, musical instruments)
- Category cues at both the acquisition and retrieval stages of learning over two trials **provides maximum storage of information** (Loewenstein, Curiel, Buschke and Duara, 2017)
- A second List of semantically related targets is presented twice with cued recall
- **A) proactive semantic interference; B) recovery from proactive semantic interference.**
- **Recovery from Proactive Interference is not measured in other memory paradigms.**





**Young**



**Aged  
(control)**



**MCI**



**Mild AD**

# MRI Volumes and Memory Impairment in 29 aMCI Participants (Loewenstein,

Curiel et al, 2017a; JAD)

(Replicated in Independent Sample of 45 aMCI participants 1Florida ADRC; Loewenstein, Curiel and Duara et al, 2017b, JAD)

	Hippocampus	Precuneus	Superior Parietal	Temporal Pole	Inferior Lateral Ventricle
List B2 Cued (frPSI)	<b><math>r = -.49^{**}</math></b>	<b><math>r = -.54^{***}</math></b>	<b><math>r = .49^{**}</math></b>	<b><math>r = .49^{**}</math></b>	<b><math>r = -.51^{**}</math></b>
HVLT-R Delayed Recall	$r = -.09$	$r = -.10$	$r = .01$	$r = -.01$	$r = -.07$
NACC Delayed Passage	$r = -.14$	$r = -.02$	$r = -.04$	$r = -.04$	$r = -.10$



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# PSI and frPSI is not limited to Cued Recall Alone

- Semantic Intrusions (either intrusions from the original target list or category intrusions that are not part of either list) represent further difficulties with source memory, monitoring and failure of inhibition)

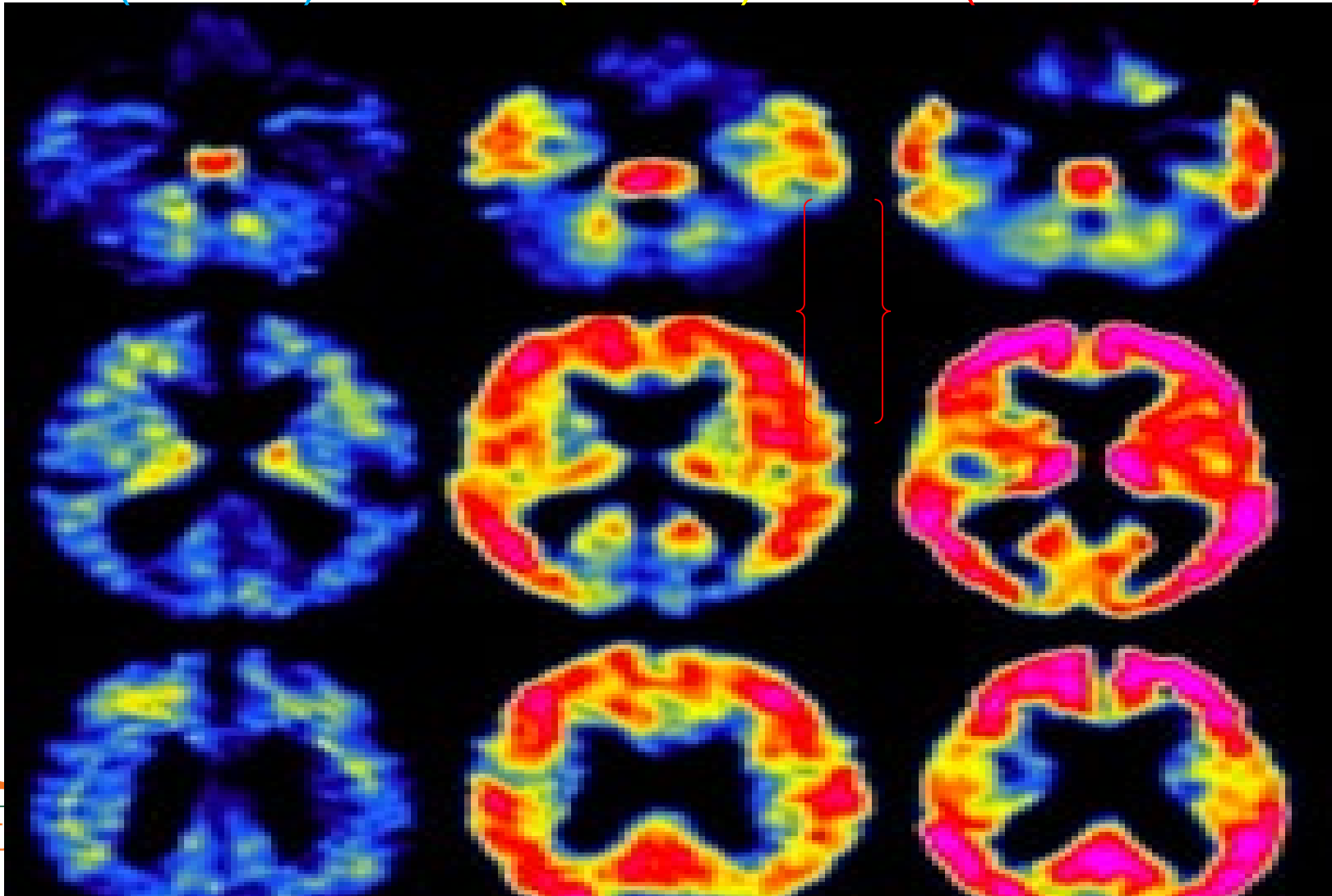


# Amyloid PET Scans: (Red is Amyloid Positive)

No Amyloid  
(Normal)

Amyloid +  
(Normal)

Amyloid ++  
(Alzheimer's)





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New Amyloid Data and the LASSI-L (Loewenstein, Curiel. DeKosky, Duara et al, Neurology, September, 2018)

- **MCI-AD (Amyloid Positive) N=34**
- **SNAP (Amyloid Negative HPC Atrophy+) N=29**
- **MCI- Other Etiologies (Amyloid Negative) N=25** (This group included patients with cerebrovascular disease, DLBD, FTD, CTE, Mass Effect of Angioma, Depression, Other Psychiatric Conditions and NOS)



	MCI-AD Amyloid+ (n=34)	MCI- SNAP (Amyloid- (HPC+) (n=29)	MCI- Non- Alzheimer's (Amyloid-) (n=25)	F-Test or X <sup>2</sup> Test	F-test Adjusting for Age, MMSE and Language
<b>HVLT-R Total</b>	16.77 (SD=5.0)	18.00 (SD=3.6)	17.88 (SD=7.3)	4.44 (.643)	.09 (p=.917)
<b>Category Fluency</b>	35.97 (SD=9.0)	35.58 (SD=8.6)	34.31 (SD=9.7)	.18 (p=.84)	1.01 (p=.371)
<b>Trails B Time</b>	157.63 (SD=72.8)	172.75 (SD=83.9)	130.00 (SD=75.4)	1.48 (.236)	.35 (p=.707)
<b>LASSI-L B1 Semantic Intrusions</b>	<b>6.50<sup>b</sup></b> <b>(SD=3.2)</b>	<b>3.00<sup>a</sup></b> <b>(SD=2.2)</b>	<b>3.41<sup>a</sup></b> <b>(SD=1.8)</b>	<b>14.52</b> <b>(p&lt;.001)</b>	<b>12.33</b> <b>(p&lt;.001)</b>
<b>LASSI-L B2 Semantic Intrusions</b>	<b>4.78<sup>b</sup></b> <b>(SD=2.5)</b>	<b>2.63<sup>a</sup></b> <b>(SD=2.2)</b>	<b>2.29<sup>a</sup></b> <b>(SD=1.9)</b>	<b>9.13</b> <b>(p&lt;.001)</b>	<b>6.28</b> <b>(p&lt;.001)</b>

## Association Between SUVR and LASSI-L Measures in 23 Subjects without MCI or Neuropsychological impairment (Loewenstein et al., 2016; AJGP)

	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	$r = -.29$	$r = -.15$	$r = -.08$	$r = -.20$	$r = -.36^*$

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# LASSI-L and Offspring of LOAD Patients

- Sanchez, Guinjoan et al (Journal of Alzheimer's Disease, 2017)
- 21 Clinically Asymptomatic middle aged offspring of LOAD in Argentina Versus 20 Middle Age Controls- Over 50% of O-LOAD patients had more than 1 LASSI-L Semantic Interference Intrusions (failure to recover from proactive semantic interference versus 0% for controls)



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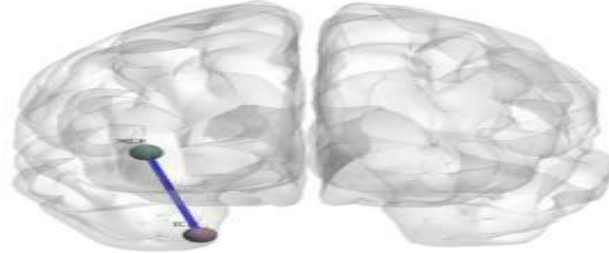
# Different fMRI Connectivity in Middle-Age Offspring of LOAD patients (O-LOAD)

- O-LOAD participants evidenced lower connectivity between entorhinal cortex and **orbitofrontal, anterior cingulate, and anterior temporal cortex.**
- In the offspring of LOAD patients, LASSI-L measures of frPSI (B2 Cued Recall) were inversely associated with connectivity between **anterodorsal thalamus** and **contralateral posterior cingulate.**
- **For O-LOAD frPSI Intrusions** on the task related to frPSI were inversely correlated with a **widespread connectivity network** involving a) **hippocampal**; b) **insular**, c) **posterior cingulate**, d) **dorsolateral prefrontal cortices**; e) **precuneii**; f) **anterior thalamus**

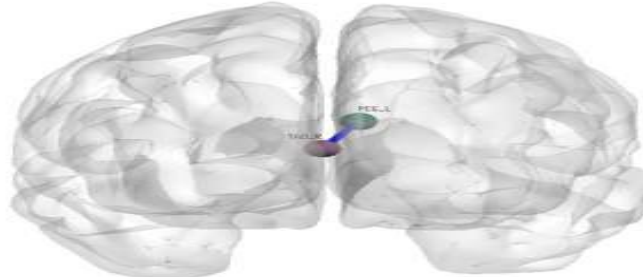


# Different fMRI Connectivity in Middle-Age OffSpring of LOAD patients

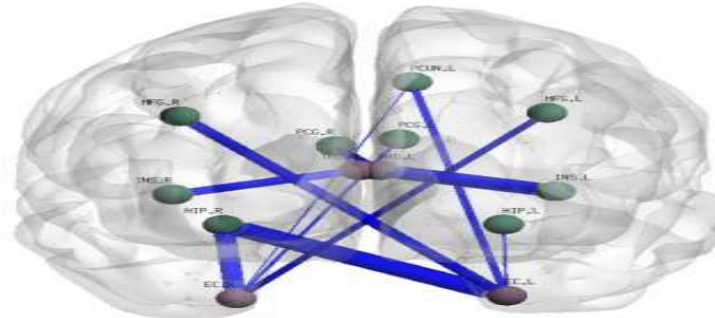
**A** Controls: Interaction ROIs vs 2B Cued Recall



**B** O-LOAD: Interaction ROIs vs 2B Cued Recall

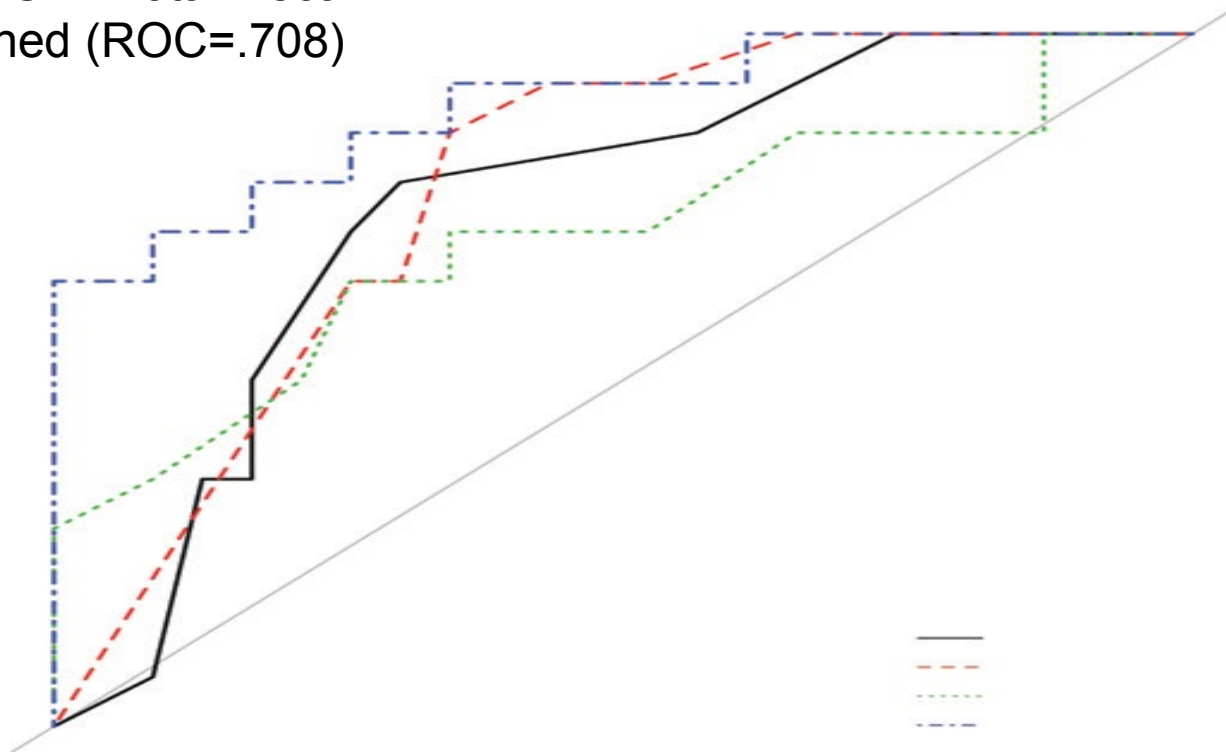


**O-LOAD: Interaction ROIs vs 2B Cued Intrusions**



# Comparison of Areas Under the ROC Curve Between LASSI-L and Free And Cued Selective Reminding Test (FCSRT) for Identifying MCI patients with FDG PET AD Patterns (Matias- Guiu et al, 2018; JAD)

- LASSI-L- frPSI and --- LASSI-L Delayed recall Combined (ROC=.894)
- FCSRT Delayed Recall and --- FCSRT Total Recall Combined (ROC=.708)



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# Potential Importance of Our Ongoing Work

- What is normal versus abnormal memory, other cognitive decline
- Can newly developed measures detect the earliest changes going on in the brain and the central nervous system early than traditional cognitive measures.
- Can early detection lead to earlier, more effective interventions and prevention strategies?





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  - 7AZL18 DA Loewenstein PI
  - 8ALZ23 DA Loewenstein PI