"Cognitive Stress' Test Paradigms, Biomarkers and Detection of Early Alzheimer's Disease

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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.
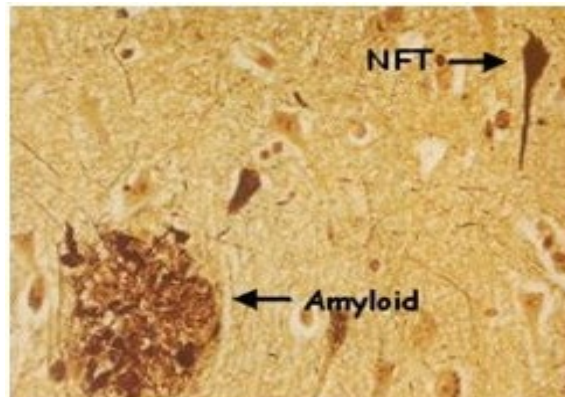
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Neuropathology of Alzheimer's
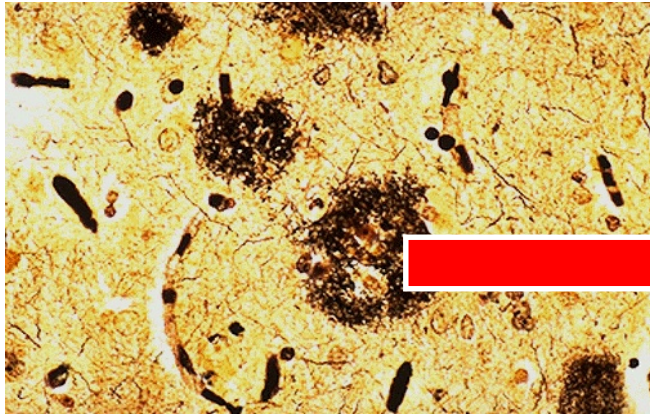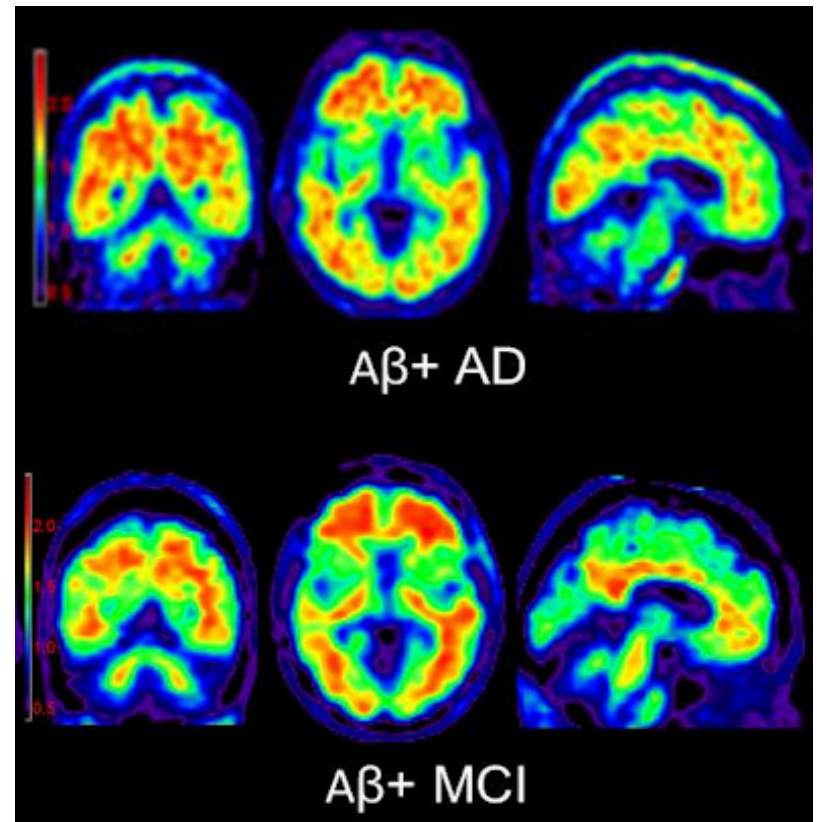

Plaques
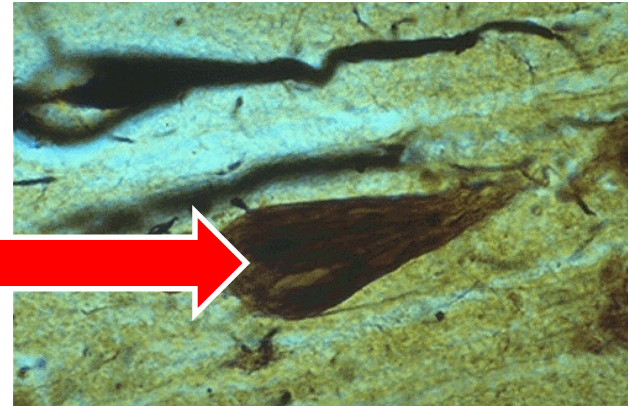
Tangles

Young

Aged
(control)

MCI

Mild Alzh.

PET Amyloid Imaging
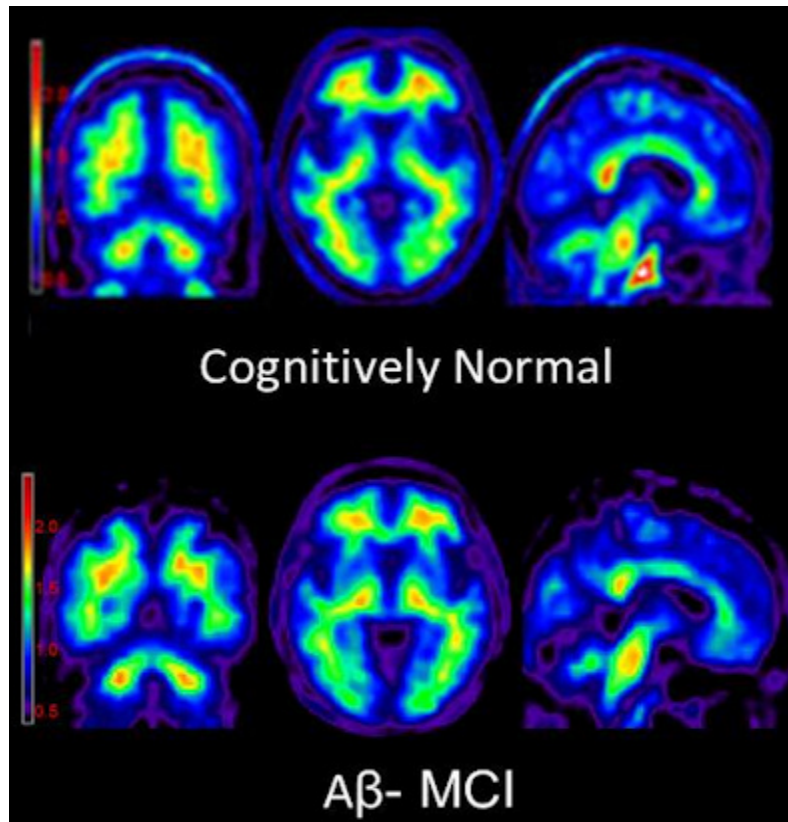
Tau Imaging
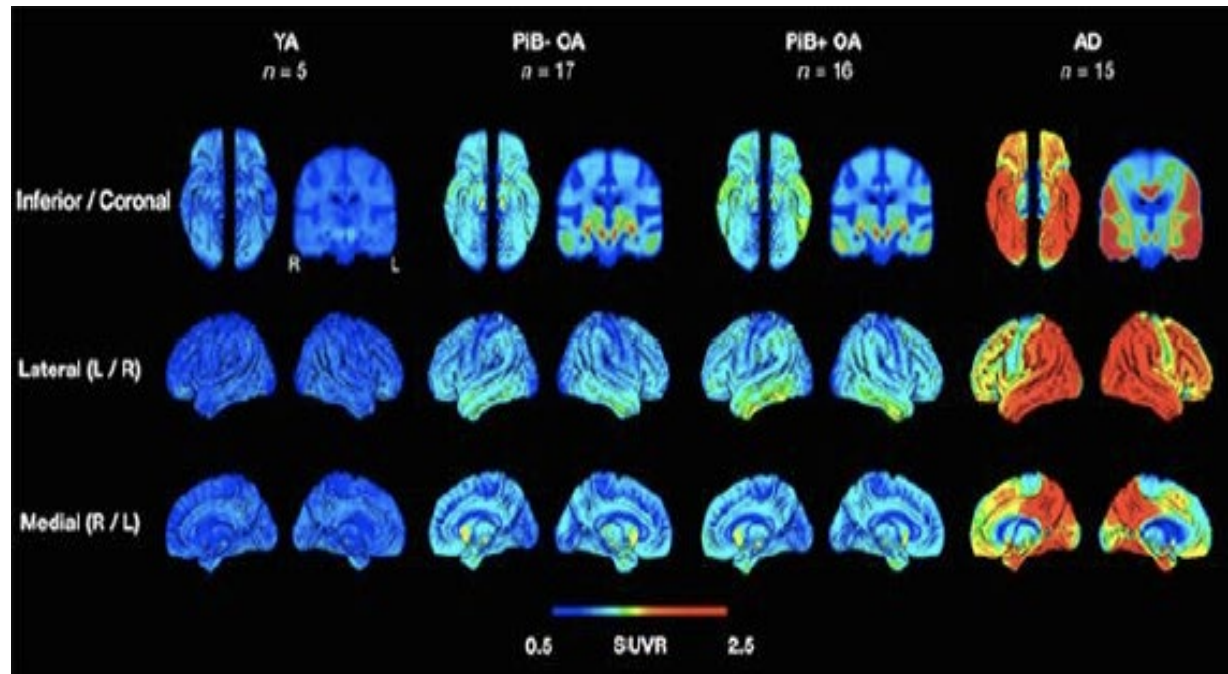
Cerebrospinal Fluid Markers

- CSFAß

- Total tau: tangle formation and the severity of neuronal damage

- Phosphorylated tau: prodromal AD

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Limitations of Biomarkers

- Expensive

- Not Readily Available

- Emerging Therapies and Prevention Trials by. the FDA Depend on Meaningful Clinical, Cognitive and Functional Endpoints

- There may a 15-20 year window between amyloid deposition and clinical symptoms and some people with significant amyloid load will not exhibit clinical symptoms during life

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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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Cognitive Stress Tests

We refer to our measures as "**cognitive stress tests**" since they are designed to challenge the cognitive system, and have proven to be able to identify subtle memory deficits among pre-symptomatic individuals that are often not detected by traditional cognitive measures.

LASSI-L Cognitive Stress Test

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, 2018)

- 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**

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

Fruits   Clothing   Musical Instruments

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)

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Previous Published Research (See Loewenstein, Curiel, Duara and Buschke, 2018; Assessment)

- **The LASSI-L distinguishes between aMCI, PreMCI and cognitively normal participants.**

- Among aMCI participants, <u>failure to recover from proactive semantic interference</u> is **associated with decreased volumes on MRI in AD prone regions.**

- Among neuropsychologically normal elders, <u>failure to recover from proactive semantic interference</u> is most **associated with amyloid load in multiple brain regions.**
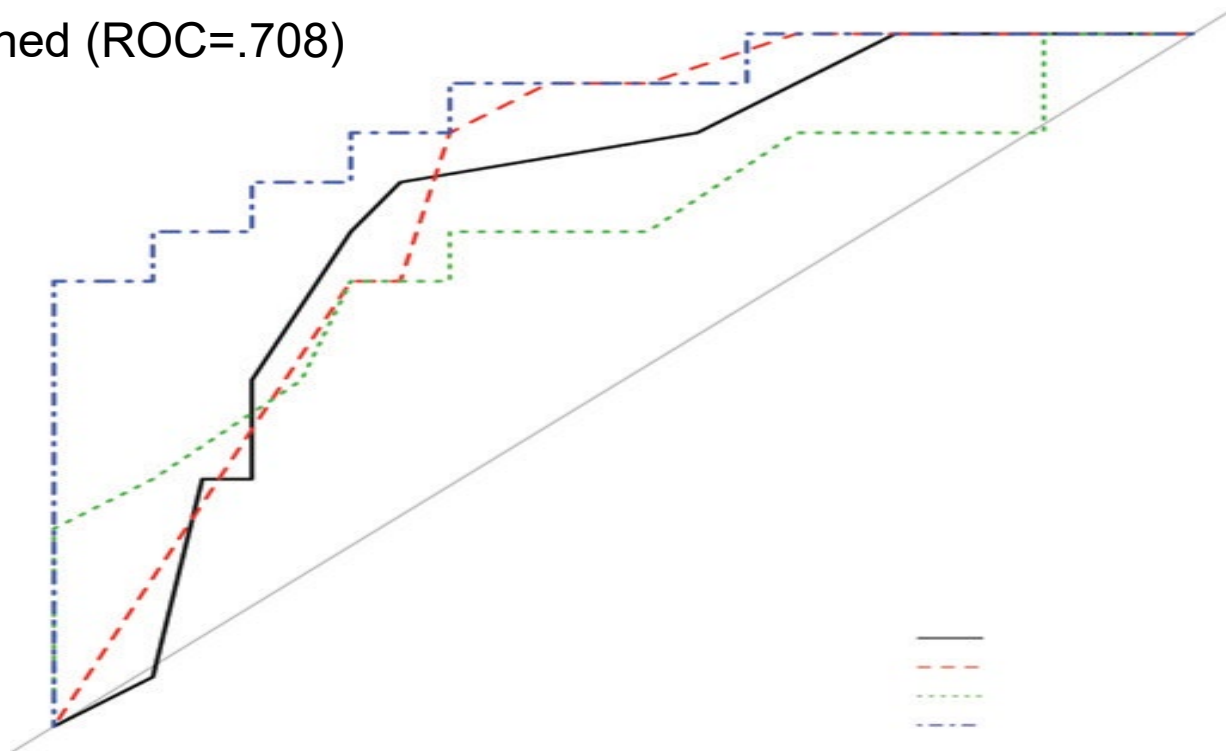
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Association Between SUVR and LASSI-L Measures in 23 Subjects without MCI or Neuropsychological impairment (Loewenstein. et al, 2016; American Journal of Geriatric Psychiatry)

	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 (frPSI)	r=-.60 **	r= -.48**	r=-.50**	r= -62**	r= -.43 *
Delayed Passages	r=-. 29	r=-.15	r=-. 08	r=-.20	r=-.36*

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)

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).

- Torres et al. (2019) found that semantic intrusions were associated with amyloid load in a community based sample on LASSI-L tests associated with PSI and frPSI.

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National Institute on Aging

Utilizing semantic intrusions to identify amyloid positivity in mild cognitive impairment

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Abstract

Objective
Semantic intrusion (SI) errors may highlight specific breakdowns in memory associated with preclinical Alzheimer disease (AD); however, there have been no investigations to determine whether SI errors occur with greater frequency in persons with amnestic mild cognitive impairment (aMCI) confirmed as amyloid positive (Amy+) vs those who have clinical symptoms of aMCI-AD with negative amyloid scans (suspected non-AD pathology [SNAP]) or persons who are diagnosed with other brain disorders affecting cognition.

Methods
Eighty-eight participants with aMCI underwent brain amyloid PET and MRI scans and were classified as early AD (Amy+), SNAP (Amy−), or other neurological/psychiatric diagnosis (Amy−). We focused on SI on the Loewenstein-Acevedo Scales for Semantic Interference and Learning (LASSI-L) targeting proactive semantic interference (PSI; old semantic learning interferes with new semantic learning), failure to recover from PSI after an additional learning trial (frPSI), and retroactive semantic interference (new semantic learning interferes with memory for old semantic learning).

Results
SIs on measures of PSI and frPSI distinguished between Amy+ AD and SNAP and other non-AD cases. PSI and frPSI intrusions evidenced moderately high associations with reduced volumes in the entorhinal cortex, superior temporal regions, and supramarginal gyrus. No such associations were observed in cases with SNAP.

Conclusions
SIs on the LASSI-L related to PSI and frPSI uniquely differentiated Amy+ and Amy− participants with aMCI and likely reflect deficits with inhibition and source memory in preclinical AD not captured by traditional cognitive measures. This may represent a specific, noninvasive test successful at distinguishing cases with true AD from those with SNAP.

FEATURED RESEARCH

Cognitive stress test predicts high levels of beta-amyloid

September 26, 2018

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Semantic Intrusions Associated with Amyloid + in MCI due to AD

- **MCI-AD** (n=34)
  - Amyloid Positive, Clinical Features of AD, HPC Atrophy+
- **MCI-SNAP** (n=29)
  - Amyloid Negative, Clinical features of AD, HPC Atrophy+
- **MCI- Other Etiologies** (n=25)
  - Amyloid Negative, cerebrovascular disease, DLBD, FTD, CTE, Mass Effect of Angioma, Depression, Other Psychiatric Conditions and NOS)

Loewenstein, D. A., Curiel, R. E., et al. (2018). *Neurology*.

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	MCI-AD (Amyloid+) (n=34)	MCI-SNAP (Amyloid-) (HPC+) (n=29)	MCI-Non-Alzheimer's (Amyloid-) (n=25)	F-Test or X^2 Test	F-test Adjusting for Age, MMSE and Language
Age	75.44 [a] (SD=8.0)	76.42 [a] (SD=7.5)	70.53 [b] (SD=5.9)	3.49 (p=.036)	NA
HVLT-R Total	16.77 (SD=5.0)	18.00 (SD=3.6)	17.88 (SD=7.3)	.44 (.643)	.09 (p=.917)
Category Fluency	35.97 (SD=9.0)	35.58 (SD=8.6)	34.31 (SD=9.7)	.18 (p=.84)	1.01 (p=.371)
Trails B Time	157.63 (SD=72.8)	172.75 (SD=83.9)	130.00 (SD=75.4)	1.48 (.236)	.35 (p=.707)
LASSI-L B1 Semantic Intrusions	6.50[b] (SD=3.2)	3.00[a] (SD=2.2)	3.41[a] (SD=1.8)	14.52 (p<.001)	12.33 (p<.001)
LASSI-L B2 Semantic Intrusions	4.78[b] (SD=2.5)	2.63[a] (SD=2.2)	2.29[a] (SD=1.9)	9.13 (p<.001)	6.28 (p<.001)

ROC Curve
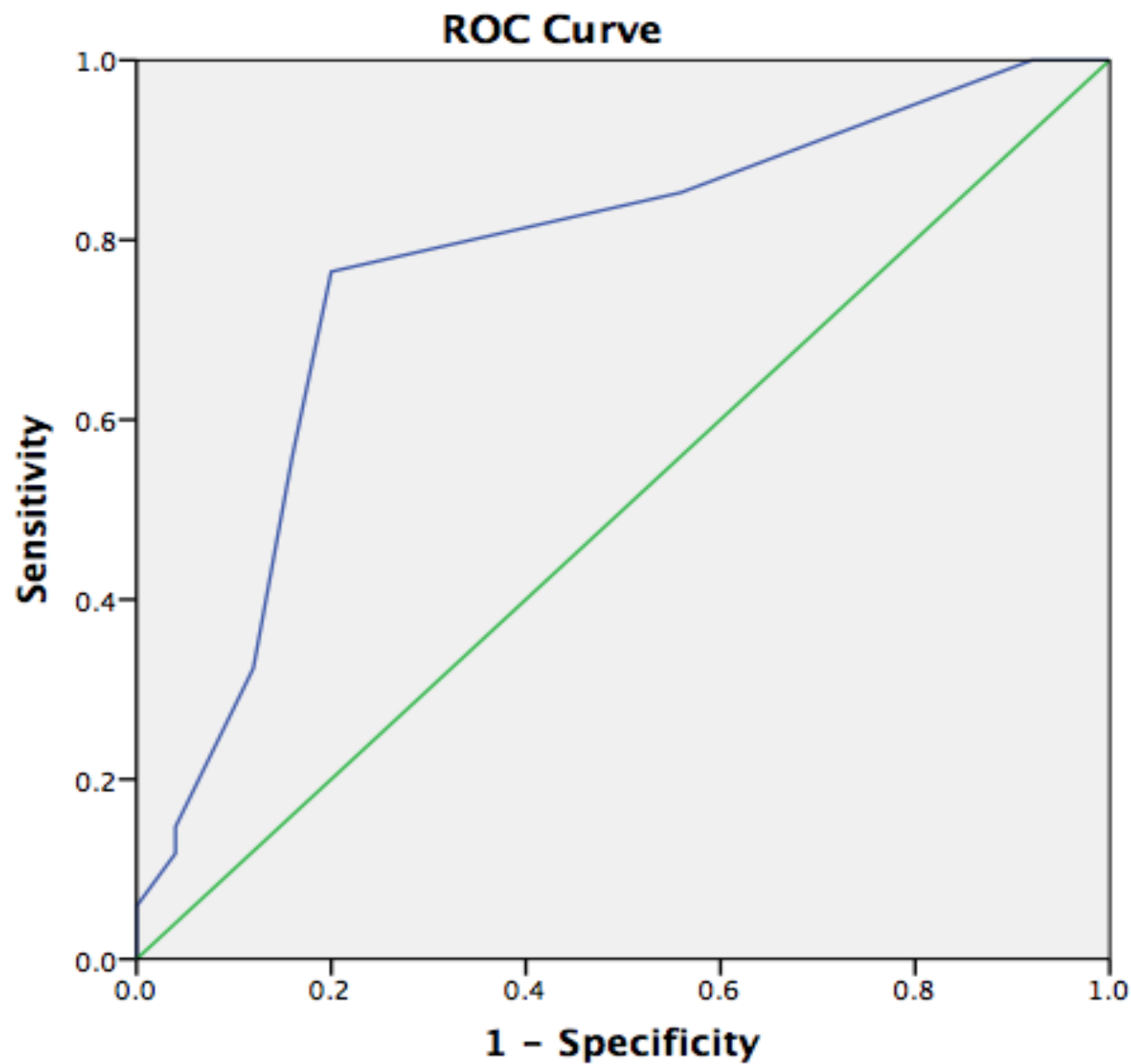
Diagonal segments are produced by ties.

LASSI-L Semantic Intrusions and Diagnostic Groups

- Results Did Not Change When Hippocampal or Entorhinal Cortex Volumes were Entered As Covariates

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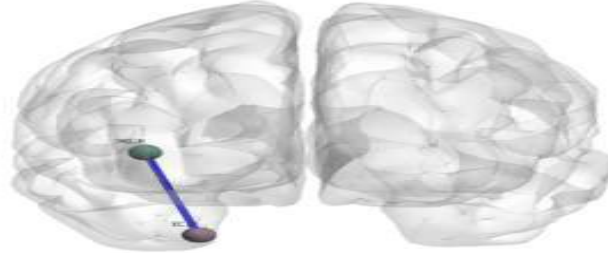
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Different fMRI Connectivity in Middle-Age OffSpring of LOAD patients (O-LOAD)

- 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) **precunei;** f) **anterior thalamus**
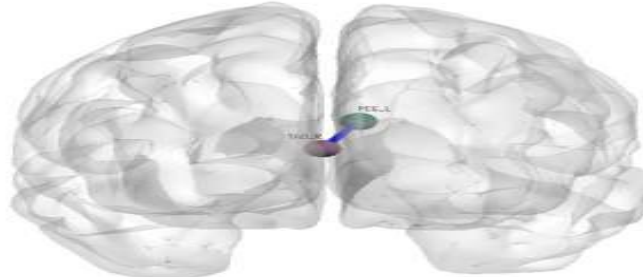
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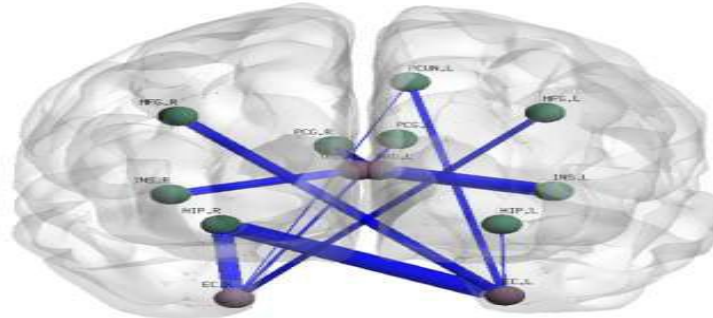# Different fMRI Connectivity in Middle-Age OffSpring of LOAD patients

LASSI-L Performance Among Hispanic and non-Hispanic Groups in Miami- N= 247 (Curiel et al, 2018)

	Non-Hisp Normals (n=62)	Hispanic Normals (n=51)	Non-Hispanic aMCI (n=71)	Hispanic aMCI (n=63)	F-Value Adjusted for Age, Sex & Ed.	p-Value
List A2 Cued Recall (Maximum Storage)	13.50 [a] (SD=1.5)	13.06 [a] (SD=1.5)	11.27 [b] (SD=2.3)	11.24 [b] (SD=2.0)	19.52	<.001
List B1 Cued Recall (PSI)	7.68 [a] (SD=2.8)	7.43 [ab] (SD=2.7	5.54 [c] (SD=2.4)	6.06 [bc] (SD=2.2)	8.44	<.001
List B2 Cued Recall (frPSI)	11.44 [a] (SD=2.3)	11.02 [a] (SD=2.2)	8.30 [c] (SD=2.5)	9.37 [b] (SD=2.2)	21.54	<.001
List A3 Cued Recall (RSI)	8.79 [a] (SD=2.4)	7.2 [b] (SD=2.1)	6.47 [b] (SD=2.0)	6.37 [b] (SD=2.0)	16.10	<.001
Delayed Free Recall for Both Target Lists A and B	19.50 [a] (SD=4.7)	18.0 [a] (SD=3.8)	13.30 [b] (SD=5.9)	13.64 [b] (SD=5.5)	20.55	<.001

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LASSI-L B2 Trial vs. HVLT-R Recall Trial as related to MRI Volumes in Participants with aMCI (Curiel et al, 2018)

	LASSI-l B2 Cued Recall Hispanic (n=25)	LASSI-l B2 Cued Recall Non-Hispanic (n=40)	HVLT-R Recall Hispanic (n=25)	HVLT-R Recall Non-Hispanic (n=40)
Hippocampus	**r=.49 ****	**r=.38 ****	r=.08	r=.23
Inferior Lateral Ventricle	**r=-.55 ****	**r=-.39 ****	r=-.31	r=-.25
Precuneus	**r=.40***	**r= .45****	r=.02	r=.14
Supramarginal	r=.28	**r= .44****	r=-.05	r=.06
Superior Temporal	r=.22	**r= .43****	r=.21	r=.17

Capp et al., 2019 – 21 African- American aMCI versus 27 African- American CN Controls Percentage of B1 Intrusion Errors (PIE)

Area Under the ROC Curve= .905
Sensitivity= 85.7% and Specificity. 81.5%

ROC Curve
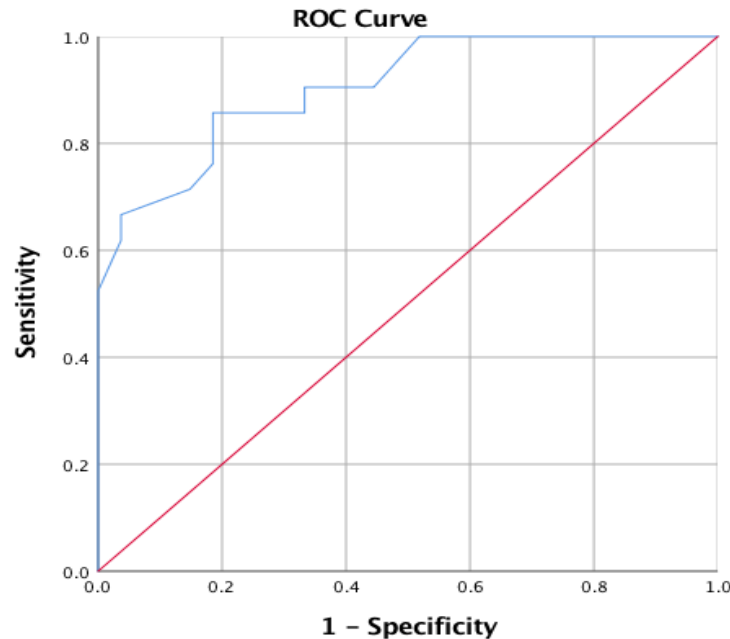
Diagonal segments are produced by ties.

Development of the Brief Computerized LASSI

- Moving into the digital age..
- State-of-the-art VR technology to automatically administer and score the test.
  - Increase accessibility
  - Promoting efficiency
  - Providing real-time data entry
  - Increase the accuracy of recording responses and response time.
- This initiative has been sponsored by the State of Florida Ed and Ethel Moore AD Research Program RO1 funding was obtained from the National Institute of Aging (Rosie Curiel-PI)

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Implication of Cognitive Stress Tests Such as LASSI-L

- Associations with biomarkers make these measures excellent tools for screening into clinical trials

- Excellent measures for early detection and progression of AD in diverse ethnic and cultural groups

- Supplying category cues at both acquisition and retrieval minimizes effects of individual learning strategies and patients serve as own controls

- Valuable endophenotype in genetic and other basic science research

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Future Directions

- **Developing and refining cognitive endophenotypes associated with preclinical AD**

- **Increasing and refining our biomarker studies (new R01 and State funded grants investigating tau agents and new cognitive stress tests (CSTs) that are extensions of the LASSI-L**

- **Technologically enhancing our cognitive assessment paradigms and validating these new computerized instruments**

- **Partnerships with academic institutions across the globe to validate our measures in other cultures and with other clinical populations**

Thank You To Our Collaborators

- The Center for Cognitive Neuroscience and Aging Team