

Cognitive Predictors of Disease Progression from Normal and At-Risk States

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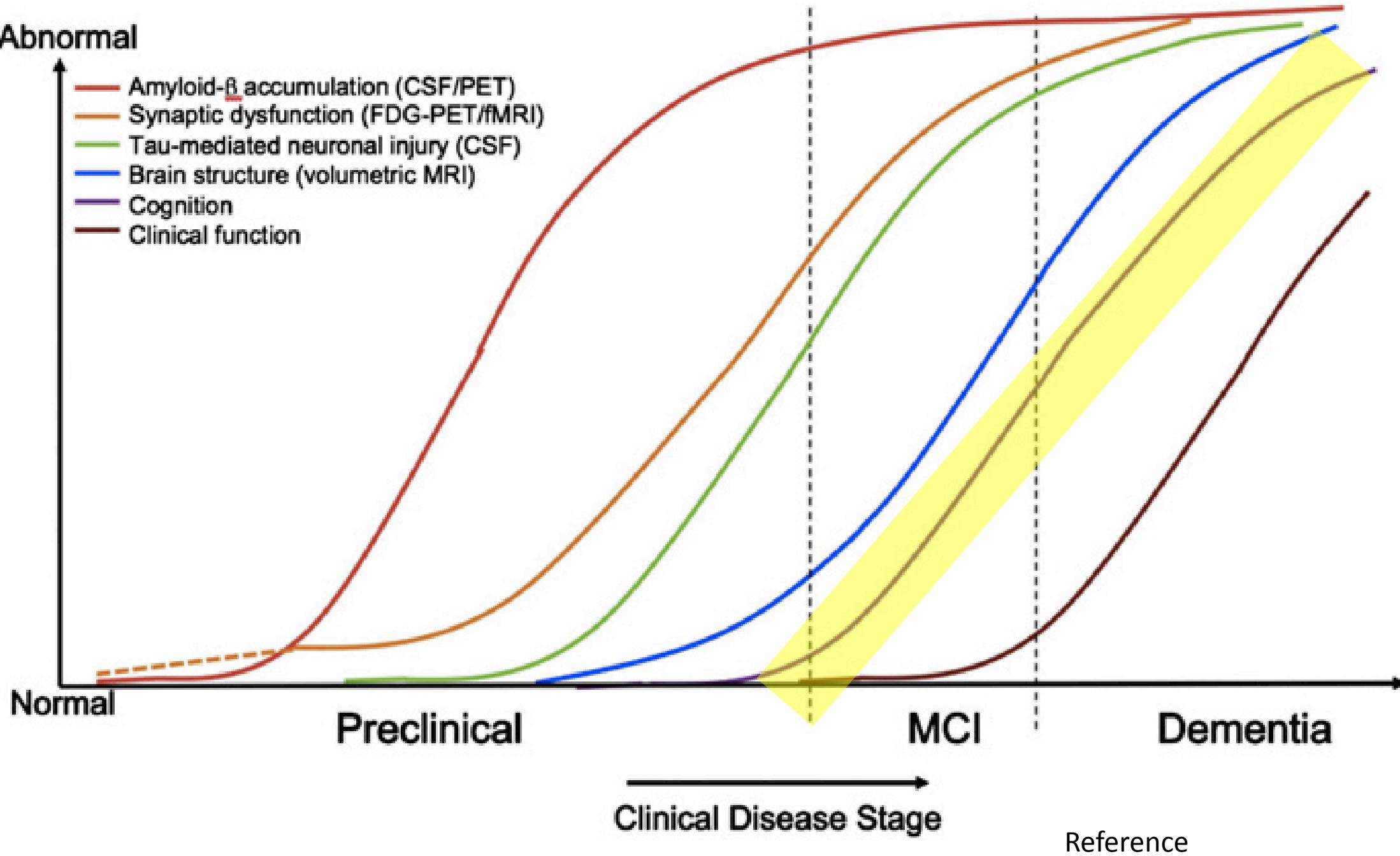
Disclosures

None.





Abnormal



Various Terms

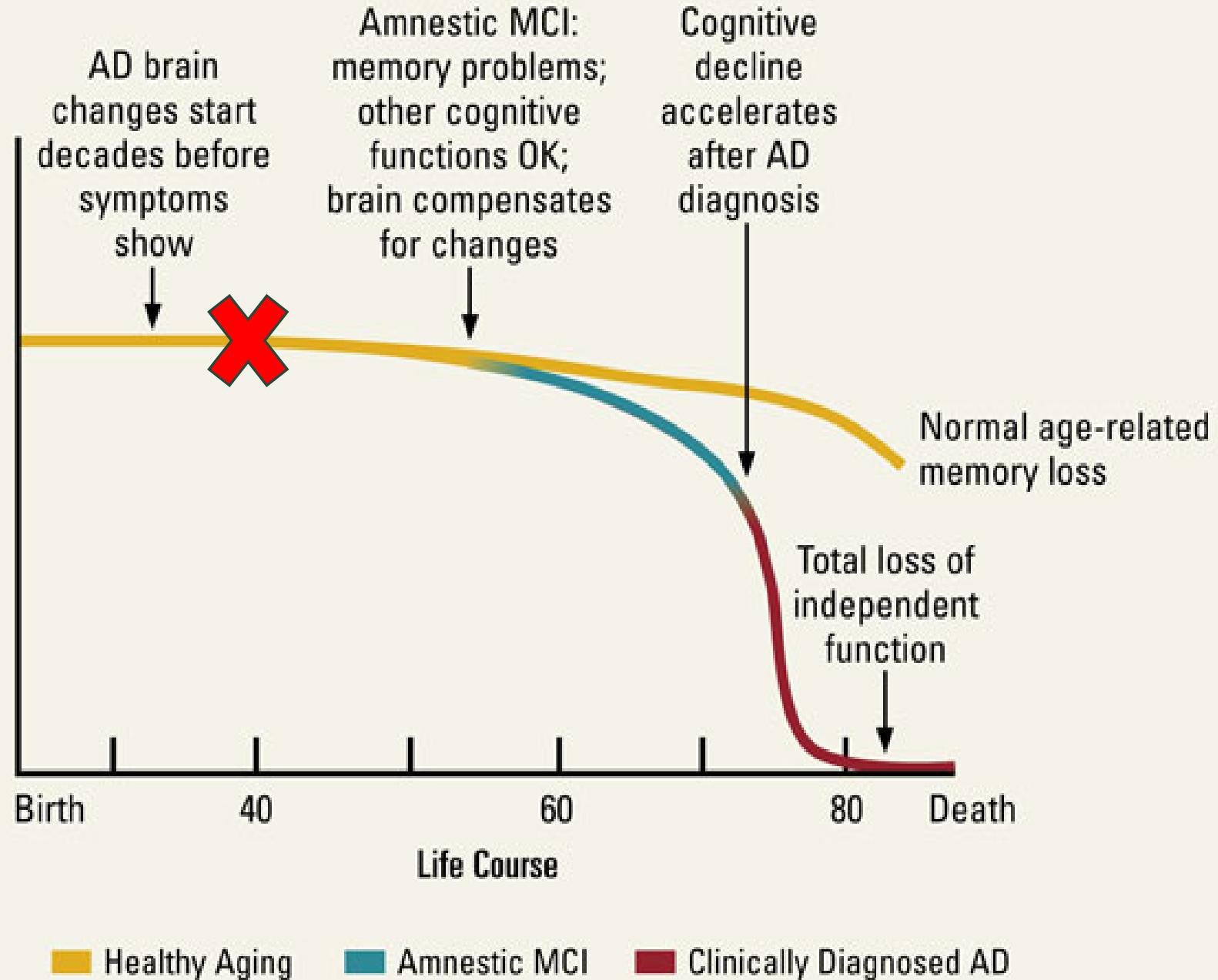
“PreMCI” (Loewenstein, Duara, et al., 2012)

“Objectively-defined Subtle Cognitive Difficulties” (Obj-SCD) (Thomas et.al, 2020)

“Impaired, not MCI” NACC Form D1 classification



Can we identify a cognitive marker during the preclinical stages of disease?



Salient Early Cognitive Markers

- ✓ Early Detection
- ✓ Associated with biomarkers of amyloidosis and neurodegeneration
 - ✓ Total and regional amyloid
 - ✓ ERC thickness
 - ✓ HPC atrophy
- ✓ Cross-culturally Valid

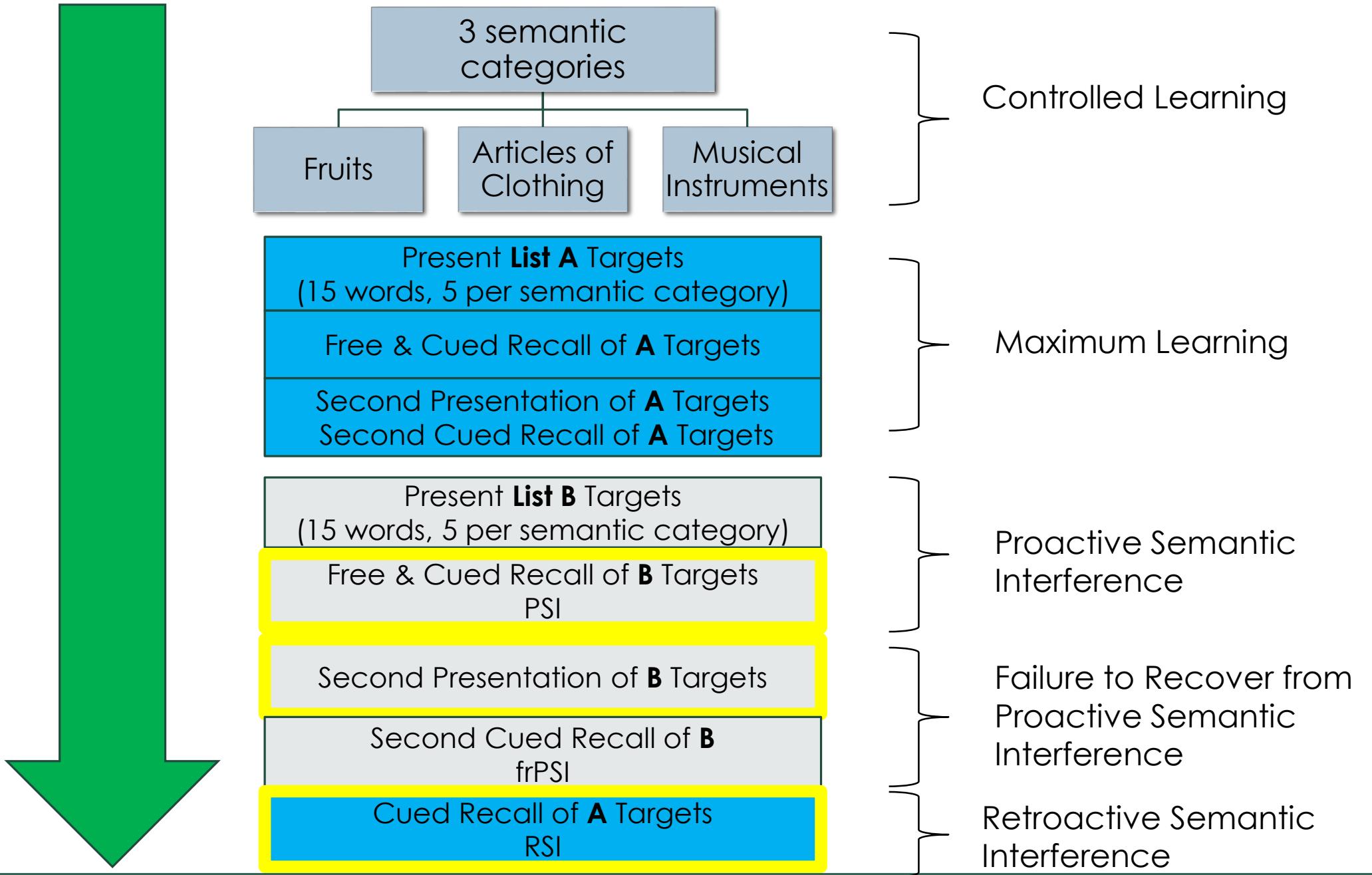
• Semantic Interference

- Proactive Semantic Interference (PSI)
- Failure to Recover from Proactive Semantic Interference (frPSI)
- Retroactive Semantic Interference(RSI)

• Semantic Intrusions(SI)



How do we measure semantic intrusion errors?



Measuring Intrusions using the LASSI-L

LIST A

SEMANTIC CATEGORY: **FRUIT**

1. apple

2. plum

3. banana

LIST B

SEMANTIC CATEGORY: **FRUIT**

1. peach

2. grapes

3. cherry

LIST B RECALL

✓ grapes

✓ peach

✗ plum

Utility of Semantic Intrusion Errors

- Semantic Intrusion errors made on memory tests may be among the earliest behavioral markers of elevated Alzheimer's disease (AD) brain pathology.
- Distinguished aMCI +Amyloid from aMCI attributable to non-AD conditions.

ARTICLE

Utilizing semantic intrusions to identify amyloid positivity in mild cognitive impairment

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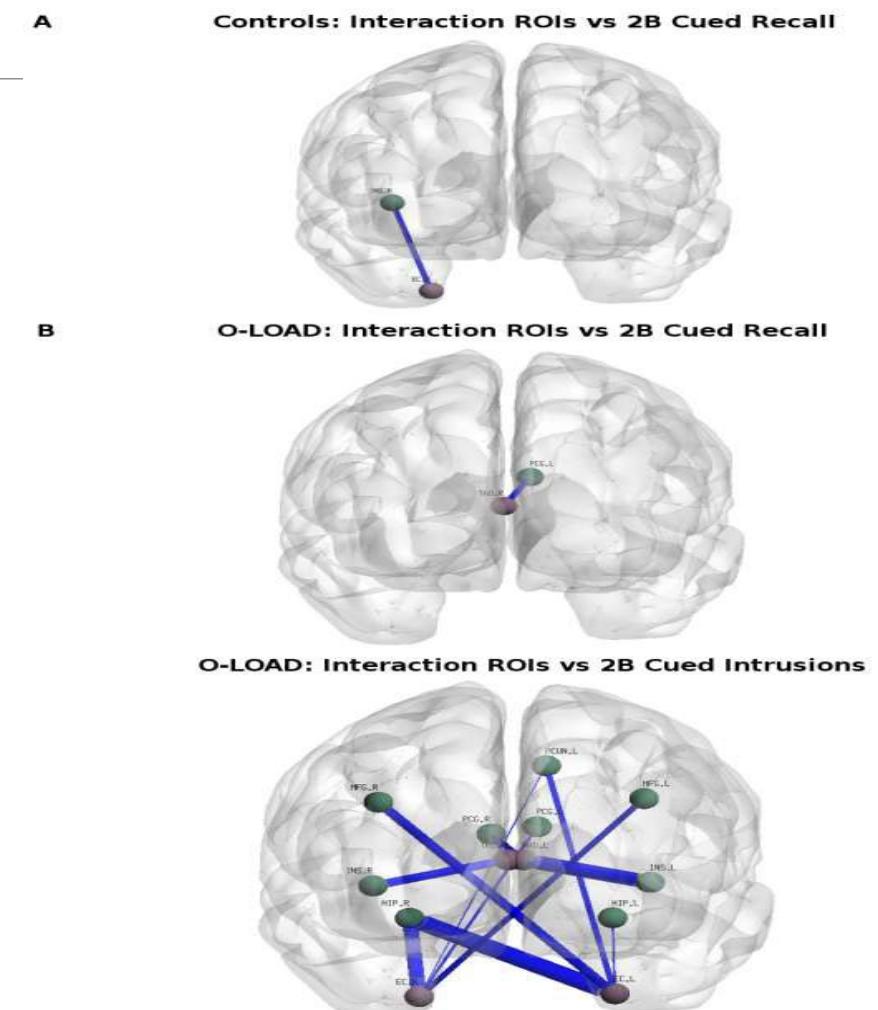
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Semantic Intrusion Errors in Asymptomatic Offspring

- Middle aged children of LOAD
- These errors were associated to functional connectivity differences compared to controls with no family history



A Clinical Observation...



- The number of intrusion errors are often highly dependent on an individual's total responses on a particular trial.
- Even a seemingly modest number of intrusions errors may represent an at-risk cognitive profile if the total number of responses are low.



LIST A

SEMANTIC CATEGORY: **FRUIT**

1. apple
2. plum
3. banana
4. mango

LIST B

SEMANTIC CATEGORY: **FRUIT**

1. peach
2. grapes
3. cherry
4. lemon

LIST B RECALL

SEMANTIC CATEGORY: **FRUIT**

- ✓ grapes
- ✓ peach
- ✗ plum
- ✗ banana

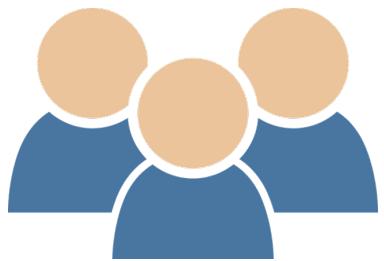
Percentage of Intrusion Errors (PIE)

Evaluates semantic intrusion errors as a function of total responses.

$$\text{PIE} = \frac{\text{Total Intrusion Errors}}{(\text{Total Intrusion Errors} + \text{Total Correct Responses})}$$

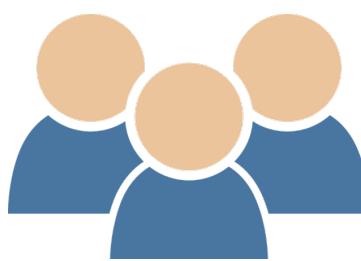


3 Diagnostic Groups



Cognitively Normal
n=21

Amyloid -



Amnestic MCI
n=72

High vs. Low
Amyloid



Early Alzheimer's
Dementia
n=31

Amyloid +



Sample Characteristics

	Cognitively Normal Amy- (n=21)	aMCI Amy- (n=36)	aMCI Amy+ (n= 36)	Mild Dementia Amy+ (n=31)	F-Value or Chi- Square	p- value
Age (52-98 Years)	69.90 (SD=6.5)	72.61 (SD=8.2)	74.80 (SD=7.3)	71.87 (SD=9.2)	1.41	.24
Education (5-22-Years)	16.05 (SD=3.0)	14.60 (SD=3.6)	14.67 (SD=3.5)	13.77 (SD=3.7)	2.29	.08
Sex % Female	57.1%	47.2 %	50.0 %	64.5 %	2. 36	.50
Tested in Spanish	47.6 %	47.2 %	40.0 %	45.2 %	.48	.92
MMSE (15-30)	29.14 ^c (SD=1.0)	27.61 ^{ab} (SD=2.6)	26.00 ^b (SD=2.4)	21.74 ^a (SD=3.6)	40.53	p<.00 1
Centiloid Value (-21.71 -216.71)	-2.17 ^a (SD=7.4)	.01 ^a (SD=8.8)	72.40 ^b (SD=25.4)	87.08 ^b (SD= 36.6)	121.07	p<.00 1

Association Between PIE and Raw Scores and Centiloid Raw Scores Among Cognitively Impaired Participants

	Centiloid Score (n=101)	Hippocampal Volume Score (n=99)	Centiloid Score Corrected for Overall Hippocampal Volume (n=91)
Cued B1 PIE (PSI)	.29** (p=.003)	-.24** (p=.018)	.35*** (p<.001)
Cued B2 PIE (frPSI)	.49 *** (p<.001)	-.20** (p=.043)	.49 *** (p<.001)
Cued A3 PIE (RSI)	.35*** (p<.001)	-.26** (p=.012)	.32** (p=.002)
Cued B1 Correct Responses	-.19 (p=.062)	.27** (p=.008)	-.17 (p=.107)
Cued B2 Correct Responses	-.39*** (p<.001)	-.36*** (p<.001)	-.31** (p=.002)
Cued A3 Correct Responses	-.23** (p=.024)	.14 (p=.160)	-.20 (p=.053)

Note: **p<0.05; ***p<0.001

Is PIE Useful to Predict Progression?

Findings

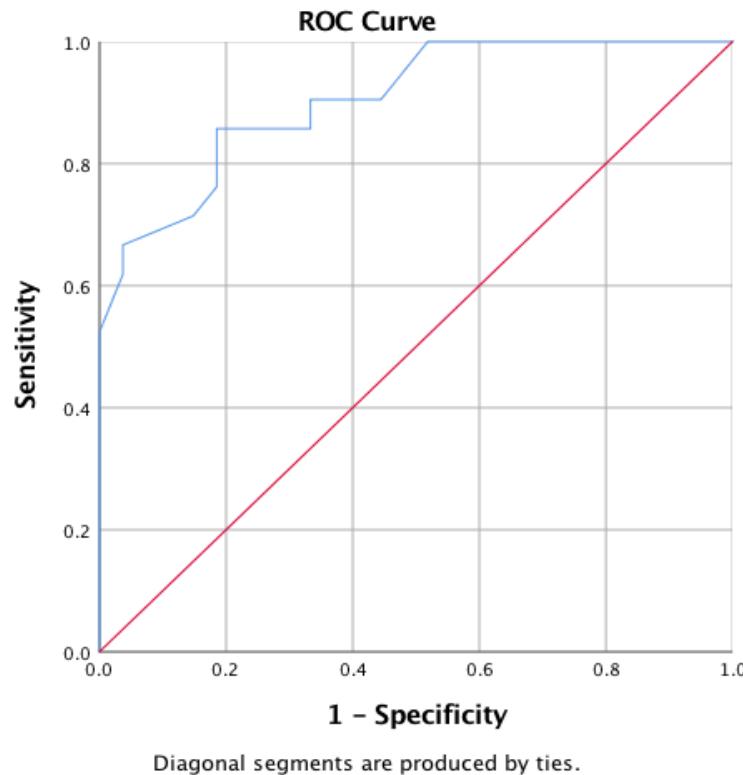
PIE accurately predicted 83.3% of aMCI who progressed to dementia.

A PIE cutpoint of 44% intrusion errors made on LASSI-L Cued B1 differentiated PreMCI participants who progressed to MCI vs. PreMCI who reverted to CN



Percentage of Semantic Intrusion Errors (PIE) Differentiates African-American aMCI versus Controls

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



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