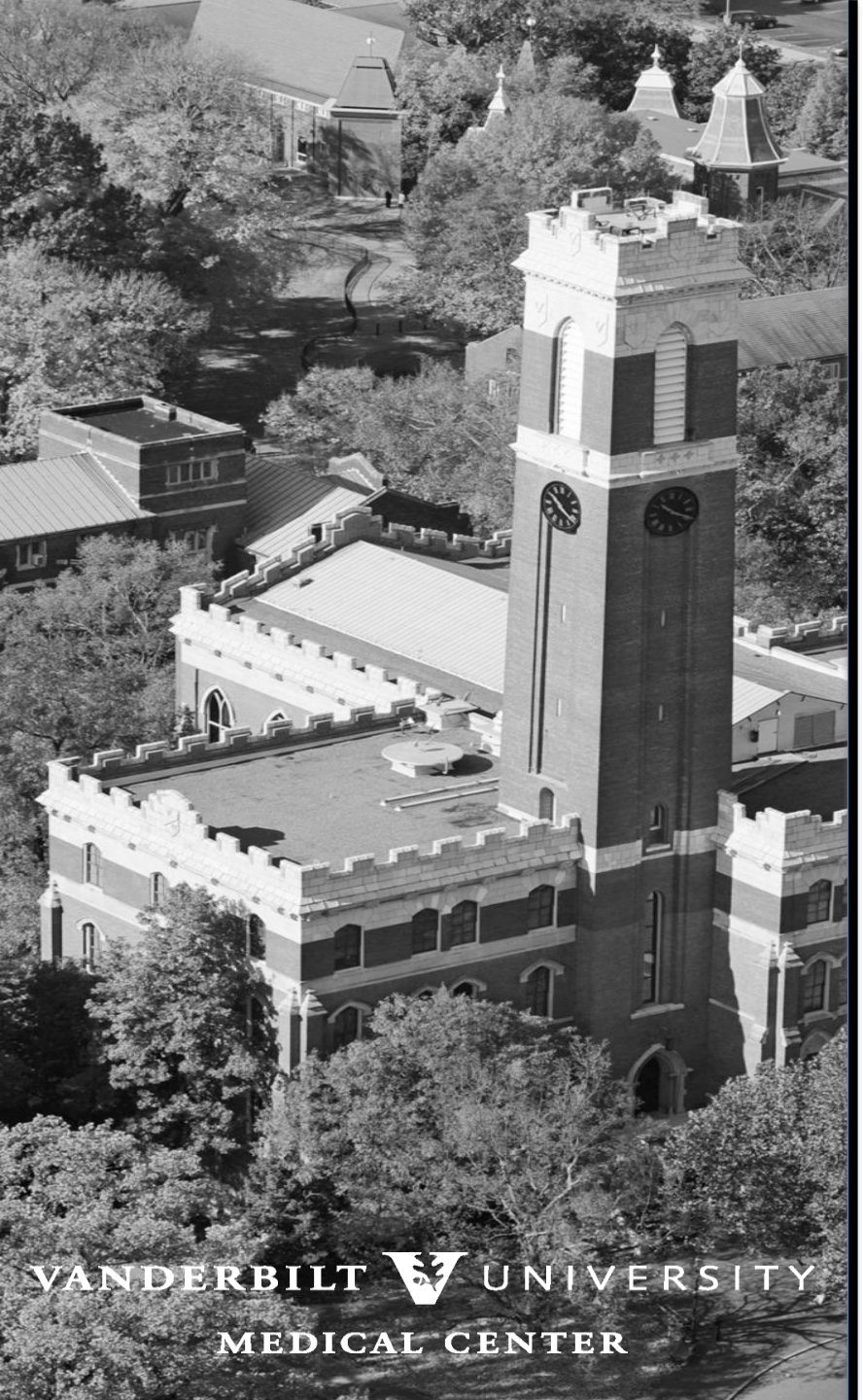


Early Detection of Alzheimer's Disease

Katherine A. Gifford, PsyD
Assistant Professor of Neurology
Clinical Neuropsychologist

Beeson Graduating Scholar (2015)
11/18/2021

Early Detection of Alzheimer's Disease

Early Detection of Alzheimer's Disease

AHEAD STUDY

The A4 Study
NOW IS THE TIME

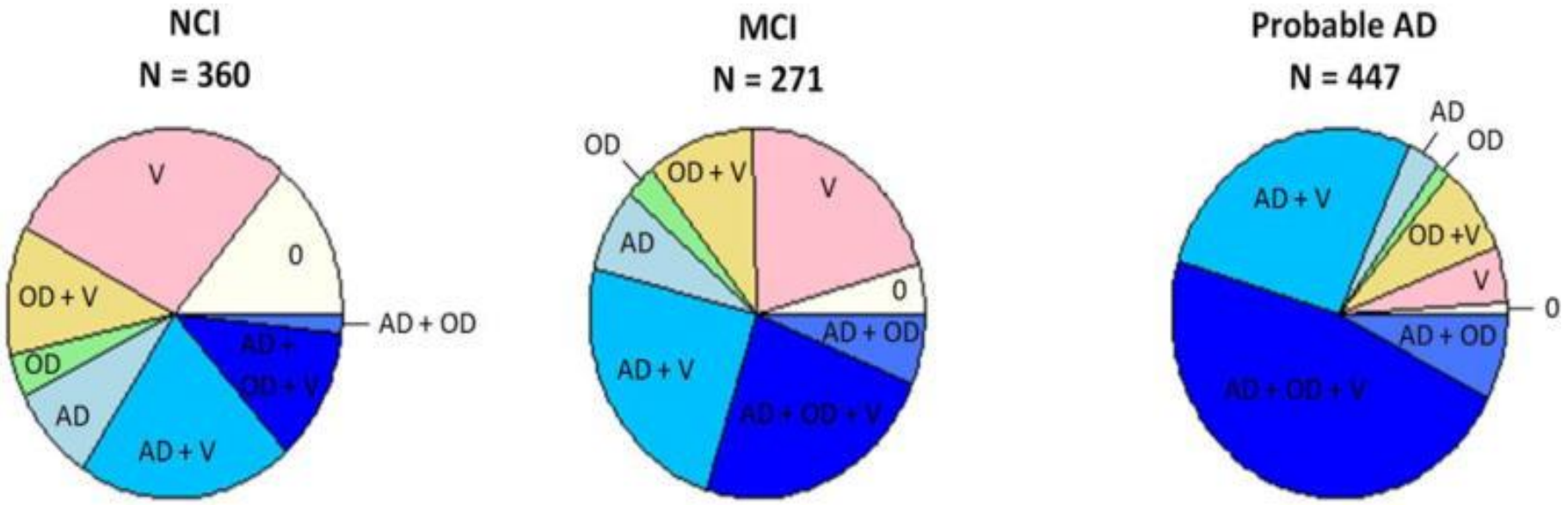
ALZHEIMER'S DRUG DONANEMAB

Lilly

Concomitant Pathways to Unhealthy Brain Aging

Alzheimer's disease and related dementia have multiple underlying pathways

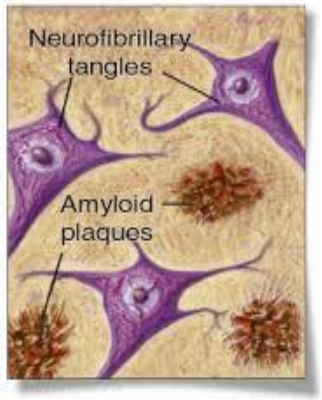
Prevalence of Pathological Processes at Autopsy in ROS/MAP



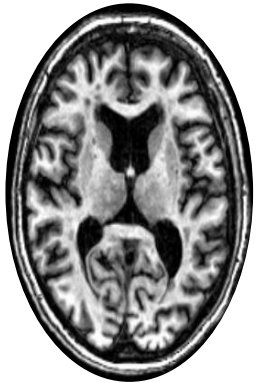
Kapasi et al., 2017, *Acta Neuropath*

Early Detection Tools

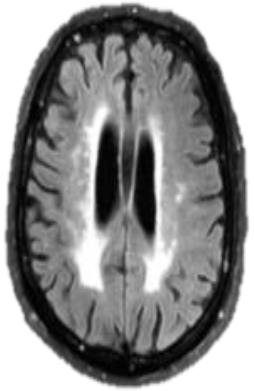
Early Detection Tools



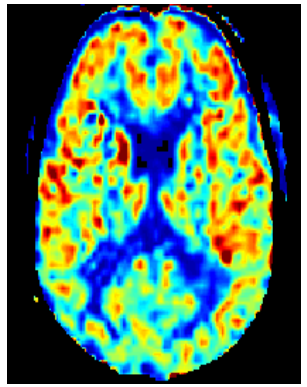
Alzheimer's Disease



Neurodegeneration



Small Vessel Disease (micro/macrostructural damage)



Cerebral Blood Flow

Sensitive to multiple pathologies early within the disease cascade

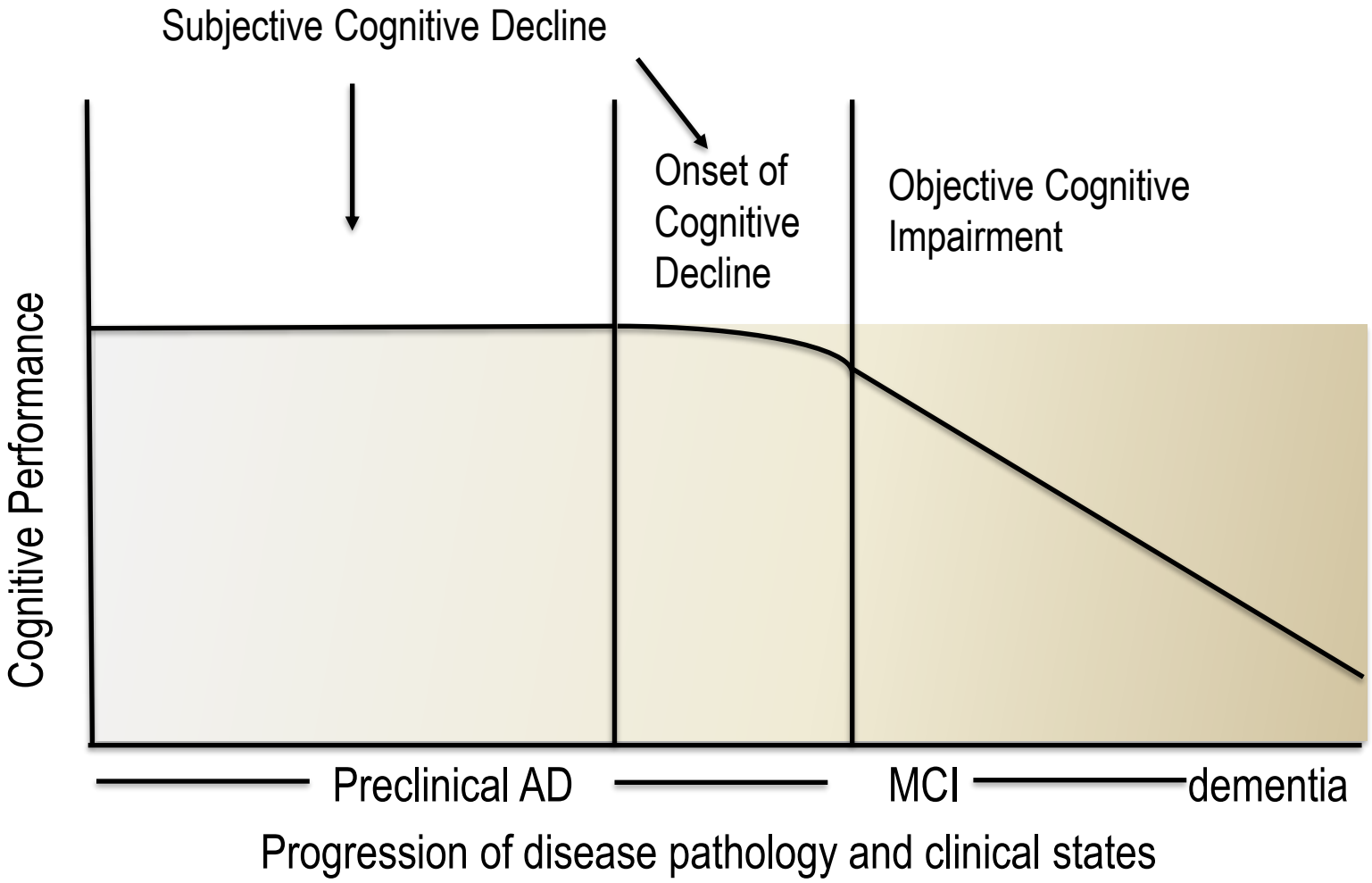
Early Detection Tools

Early Detection Tools

Sensitive to multiple early pathologies and widely accessible

Early Detection Tools: Subjective Cognitive Decline

Subjective Cognitive Decline: Concern, worry, or change in cognition reported by the patient

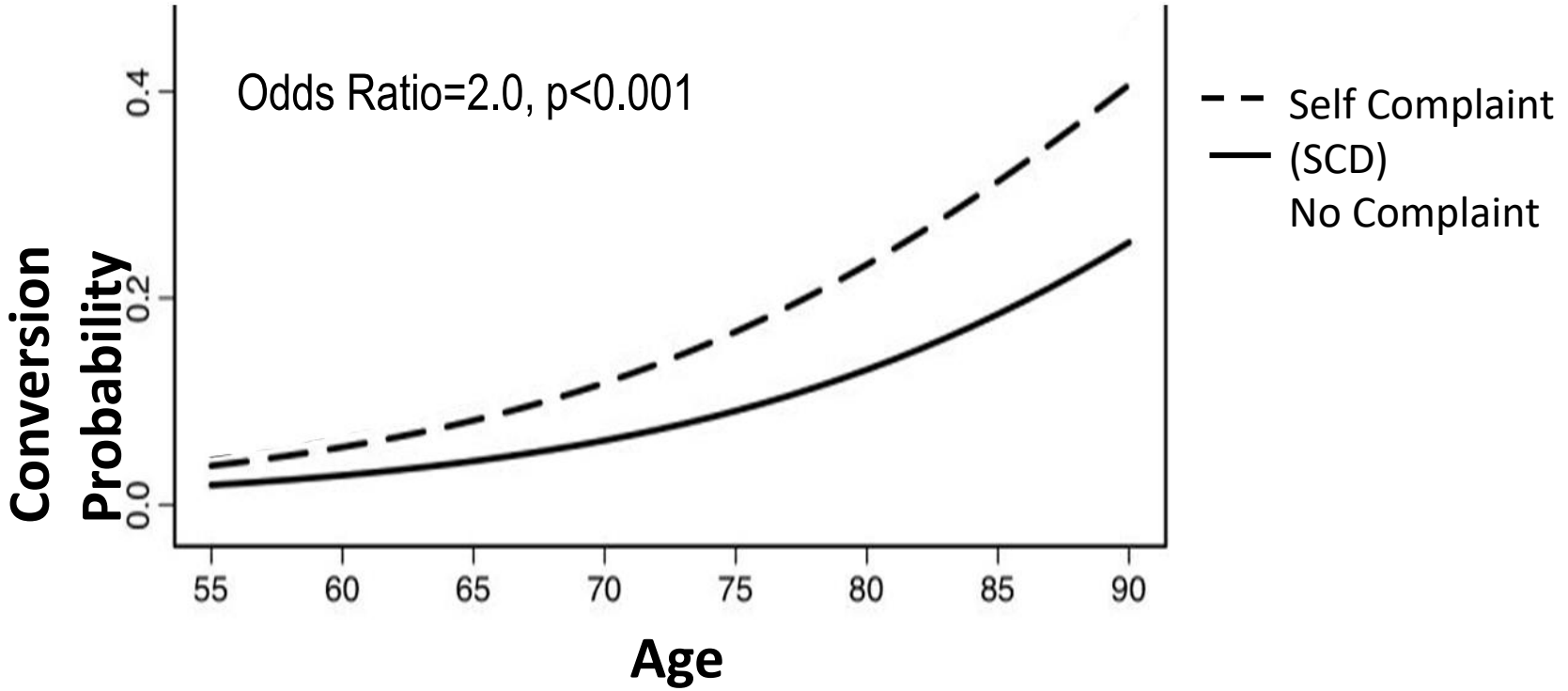


Adapted from Jessen et al., 2014, *Alzheimer's & Dementia*

SCD & Longitudinal Brain MRI

SCD is a Marker of AD

SCD predicts diagnostic conversion in cognitively normal adults

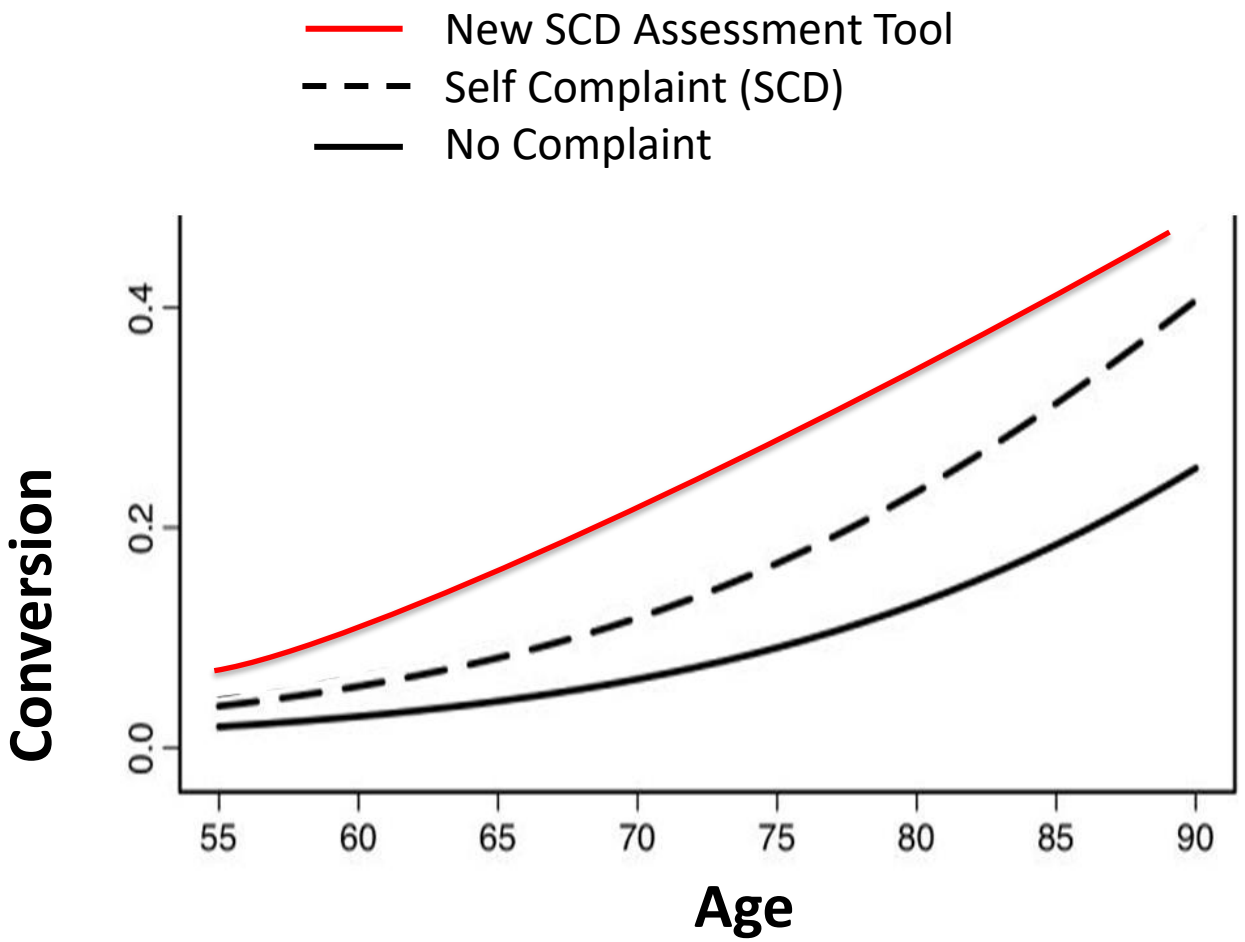


Note: National Alzheimer's Coordinating Center Data; no complaint n=2967, SCD n=585

Gifford et al., 2014, *Alzheimer's & Dementia*

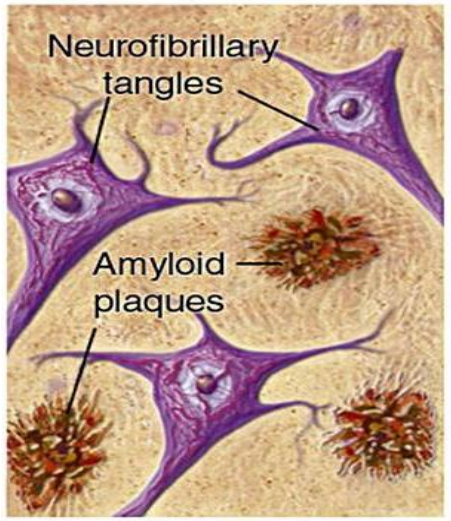
Research Aims

Enhance Use of Subjective Cognitive Decline as a Marker of Early Brain Aging



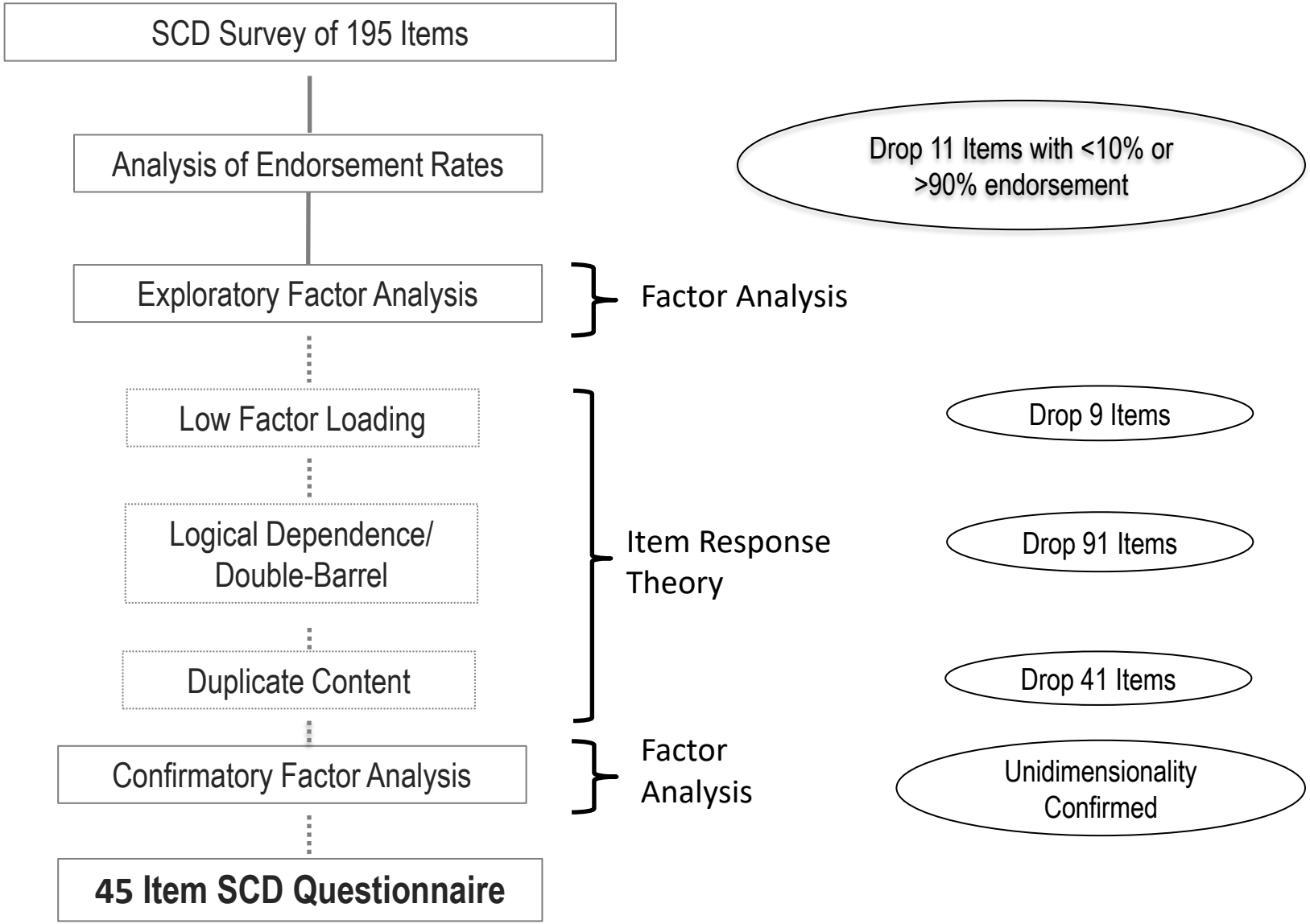
Early Detection: Merging Clinical with Biomarkers

Early Clinical Symptoms



Early Neuroanatomical and Pathological Changes

New Subjective Cognitive Decline Tool

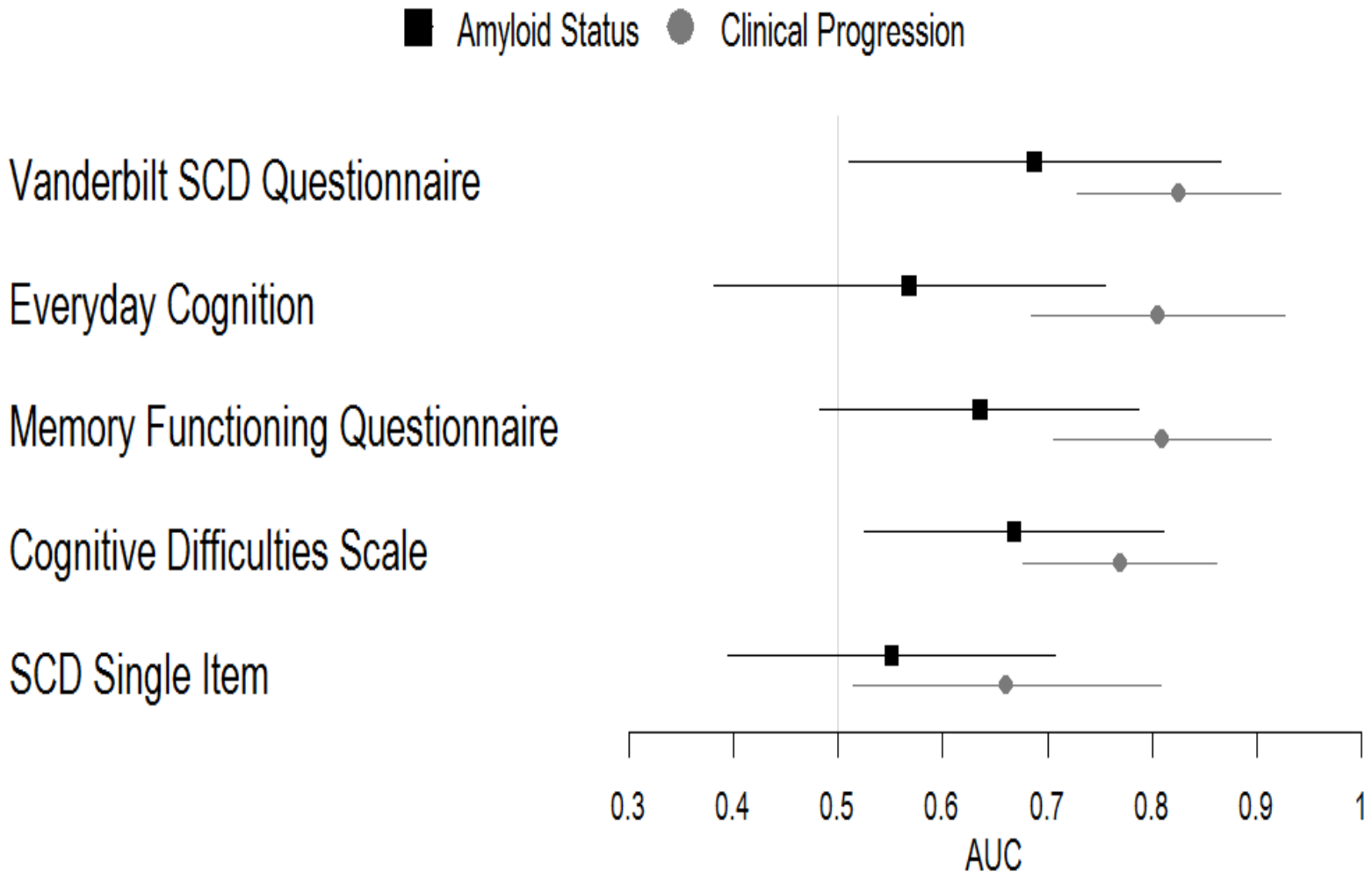


Gifford et al., 2015 *Alz Dem: DADM*
Gifford et al., 2019, *JINS*

Vanderbilt Subjective Cognitive Decline Questionnaire

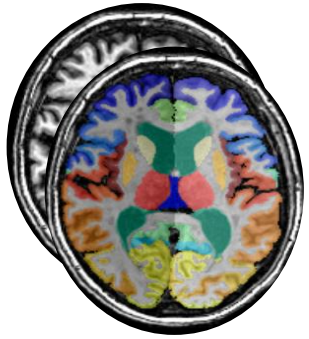
VMAP SCD Questionnaire		Score Range
Total Score		22-167 (45 items)
SCD Domain Scores	**Example Items**	**Score Range (# items)**
Memory-SCD	Do you think you have problems with your memory?	11-95 (26 items)
	I forget what day of the week it is.	
Executive Functioning-SCD	I have trouble keeping financial records organized.	4-39 (9 items)
	I have trouble thinking things through before acting.	
Language-SCD	I have trouble thinking of the names of objects.	7-33 (10 items)
	I miss the point of what other people are saying.	

Utility of the V-SCD Questionnaire: Tool Comparison



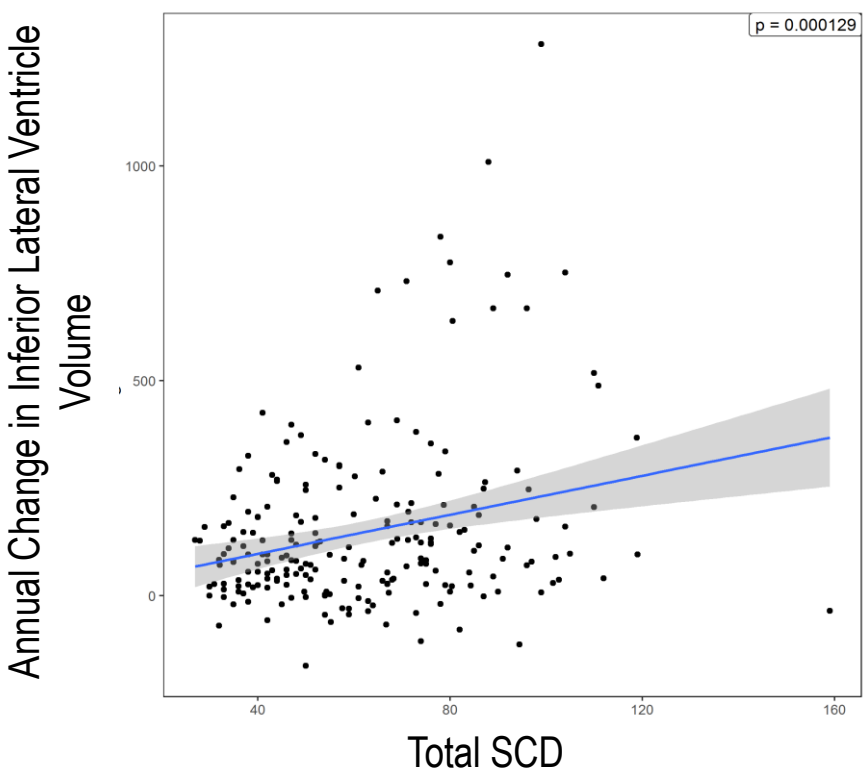
Gifford et al., 2019 *JINS*

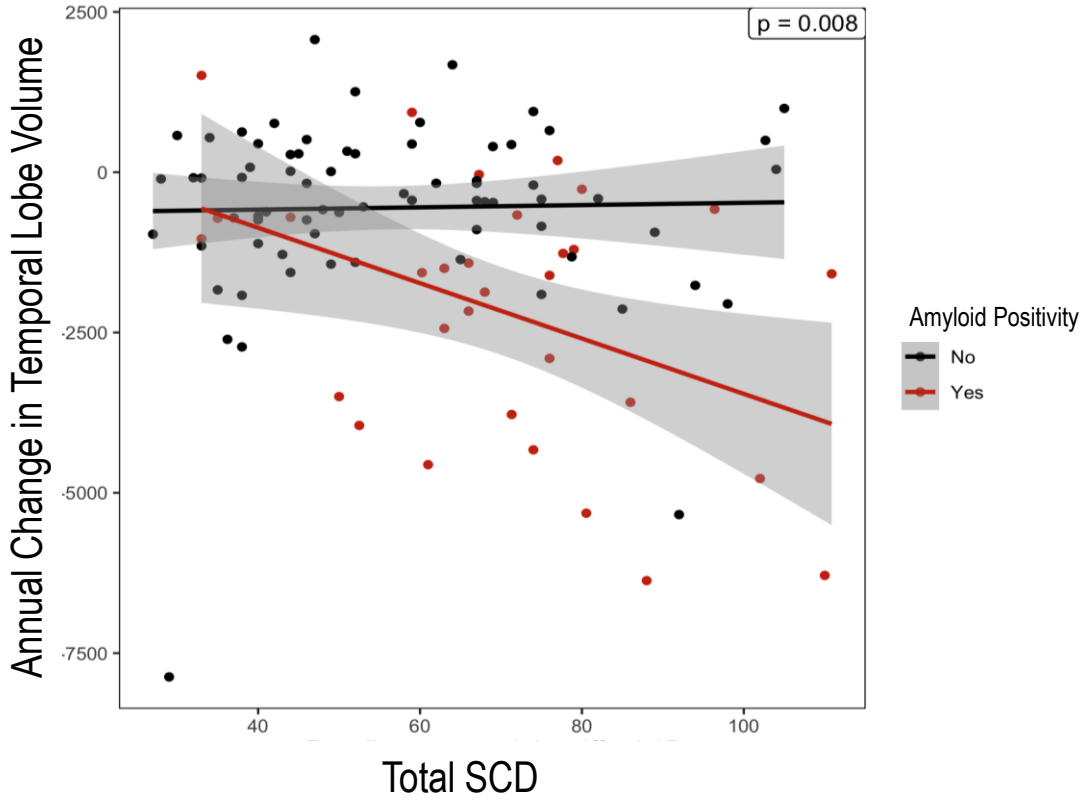
Utility of the V-SCD Questionnaire: Structural Brain MRI



T1 Multi-Atlas

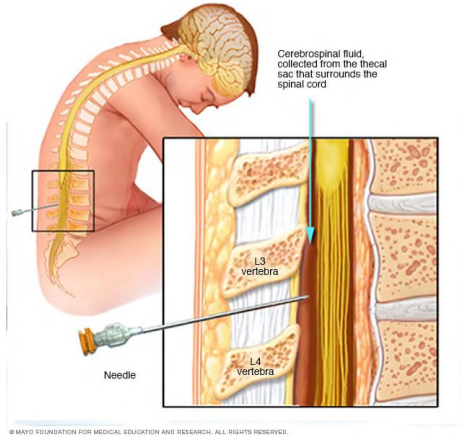
SCD is broadly and robustly associated with atrophy in the medial temporal lobe

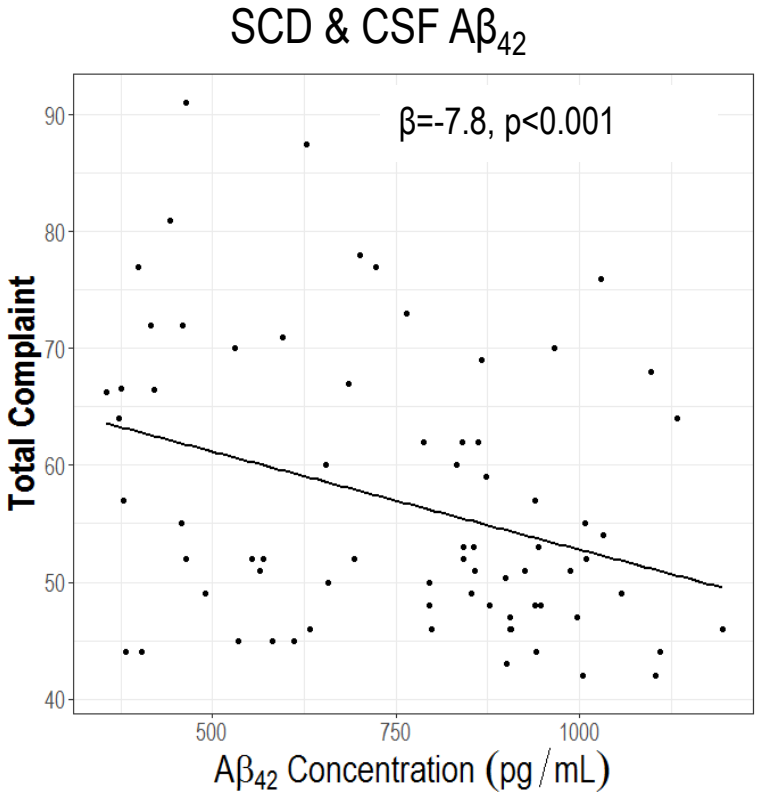




Gifford et al., 2020, Alz & Dem; Steinbach 2021, *ACN*

Utility of the V-SCD Questionnaire: CSF Biomarkers

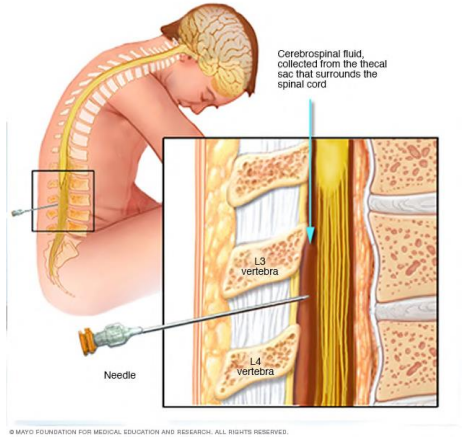




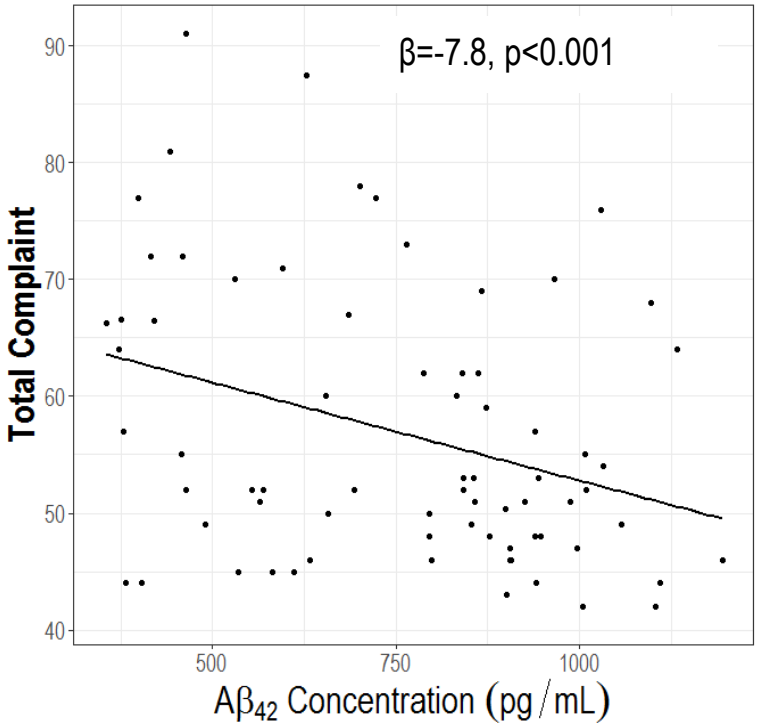
Note: $A\beta_{42}$ from fasting lumbar puncture of cognitively normal older adults

Gifford et al., 2017 *JINS*

Utility of the V-SCD Questionnaire: CSF Biomarkers

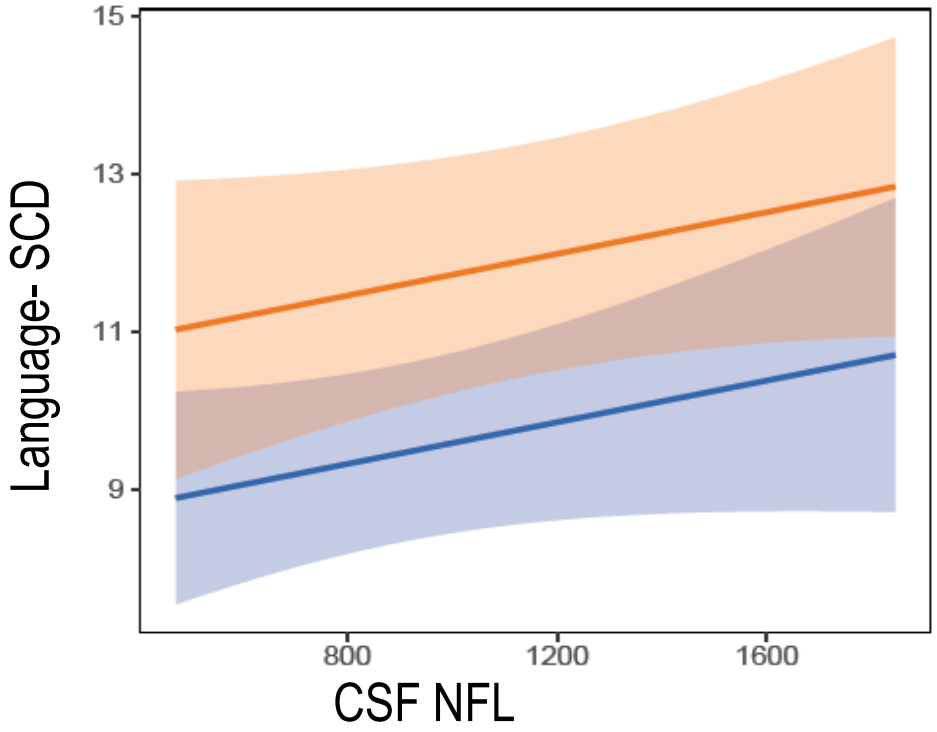


SCD & CSF $A\beta_{42}$



Note: $A\beta_{42}$ from fasting lumbar puncture of cognitively normal older adults

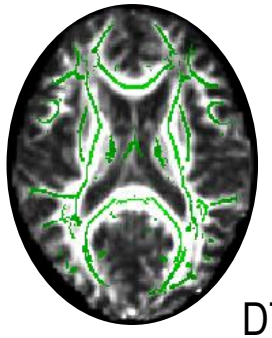
SCD & CSF NFL



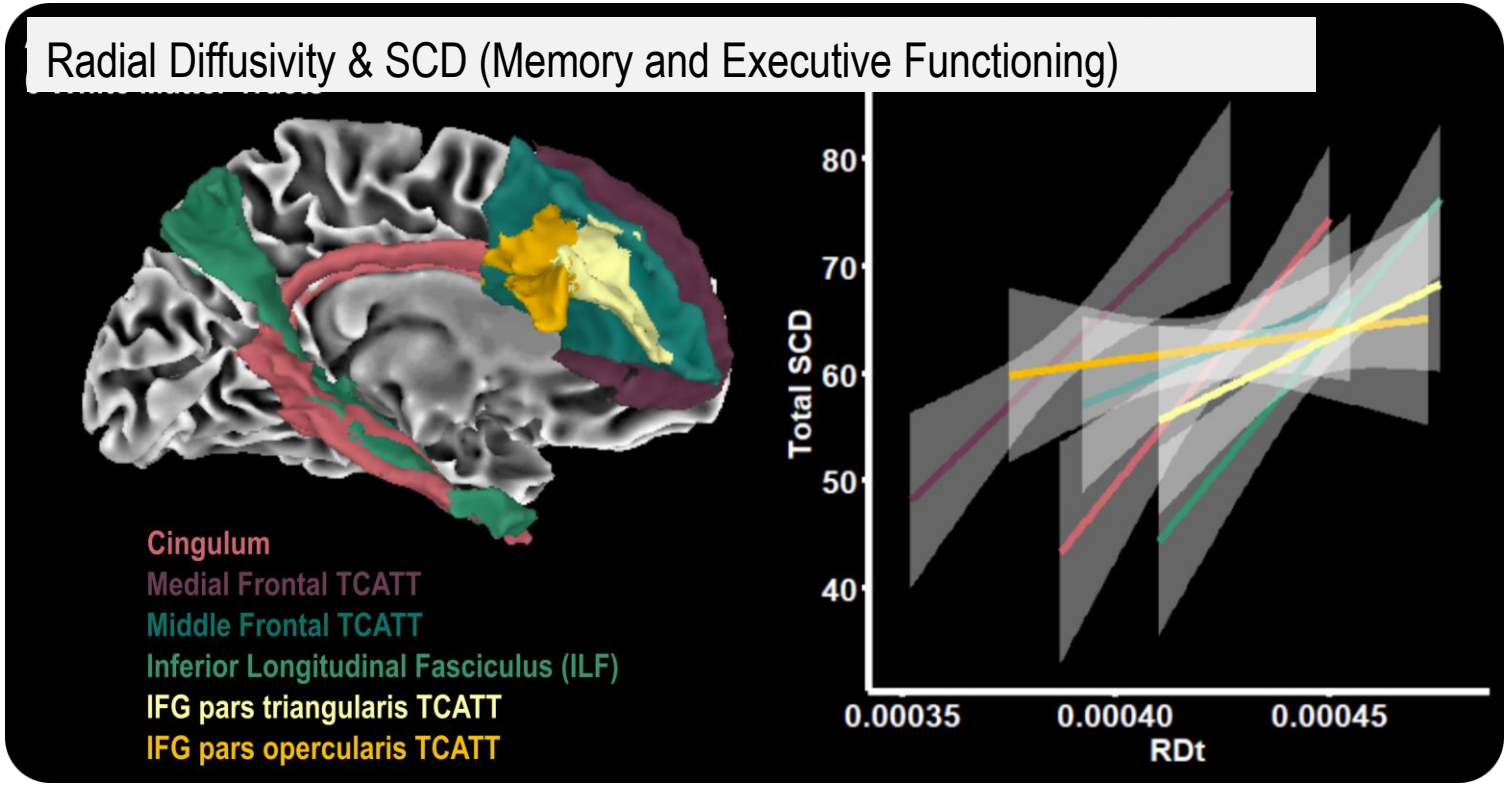
Note: blue line=NC, orange=MCI

Gifford et al., 2017 *JINS*

Utility of the V-SCD Questionnaire: White Matter Integrity

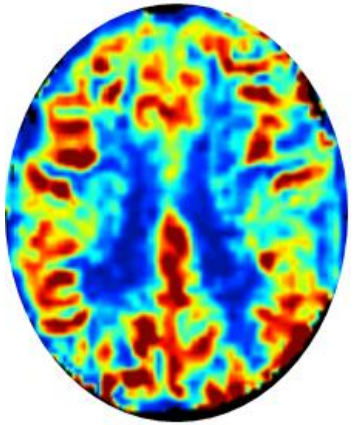


DTI TBSS

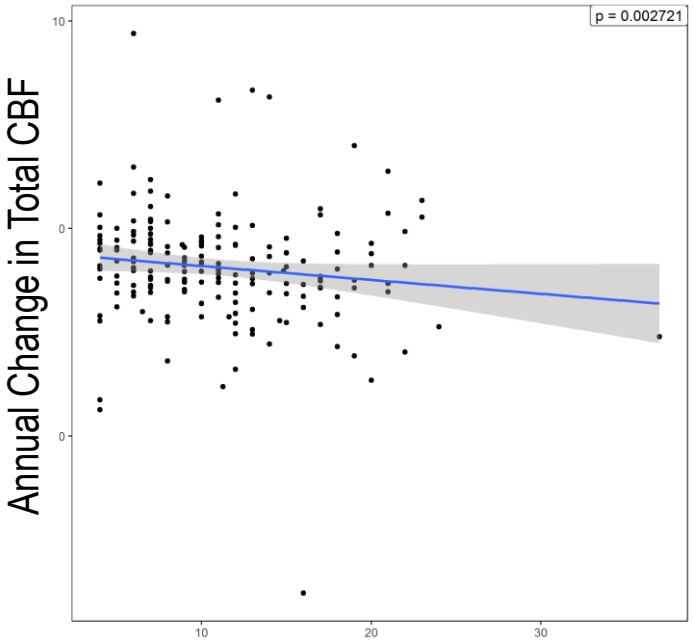


Archer, Moore et al., 2021, Neuroimage: Clinical

Utility of the V-SCD Questionnaire: Cerebral Blood Flow



pCASL
CBF

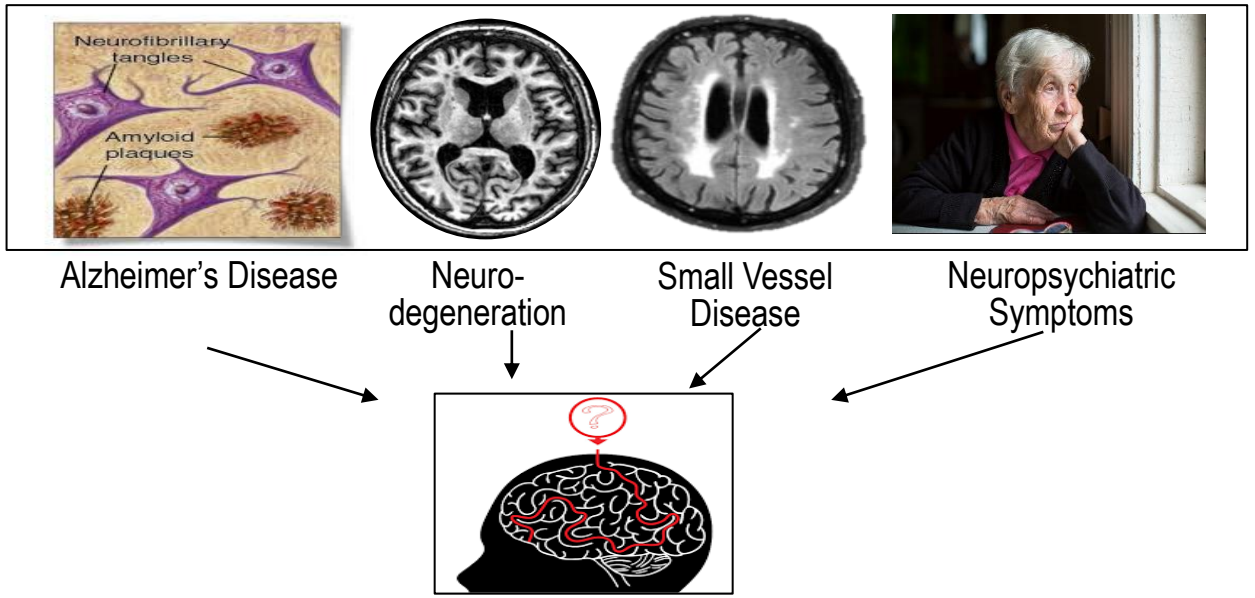


	Total CBF		Frontal Lobe CBF		Parietal Lobe CBF		Occipital Lobe CBF	
SCD Outcomes	**β**	**p-value**	**β**	**p-value**	**β**	**p-value**	**β**	**p-value**
Total SCD	**-0.01**	**0.04***	-0.01	0.05	**-0.02**	**0.03***	-0.01	0.10
Memory-SCD	-0.02	0.07	-0.02	0.08	-0.03	0.06	-0.02	0.19
Language-SCD	-0.04	0.05	-0.04	0.09	**-0.06**	**0.047***	-0.03	0.27
Executive Functioning-SCD	**-0.07**	**0.003**	**-0.07**	**0.006**	**-0.09**	**0.002**	**-0.06**	**0.01**
Note: *Results attenuated and non-significant in sensitivity analyses excluding statistical outliers								

Kresge et al., 2020 Alz & Dem

Summary

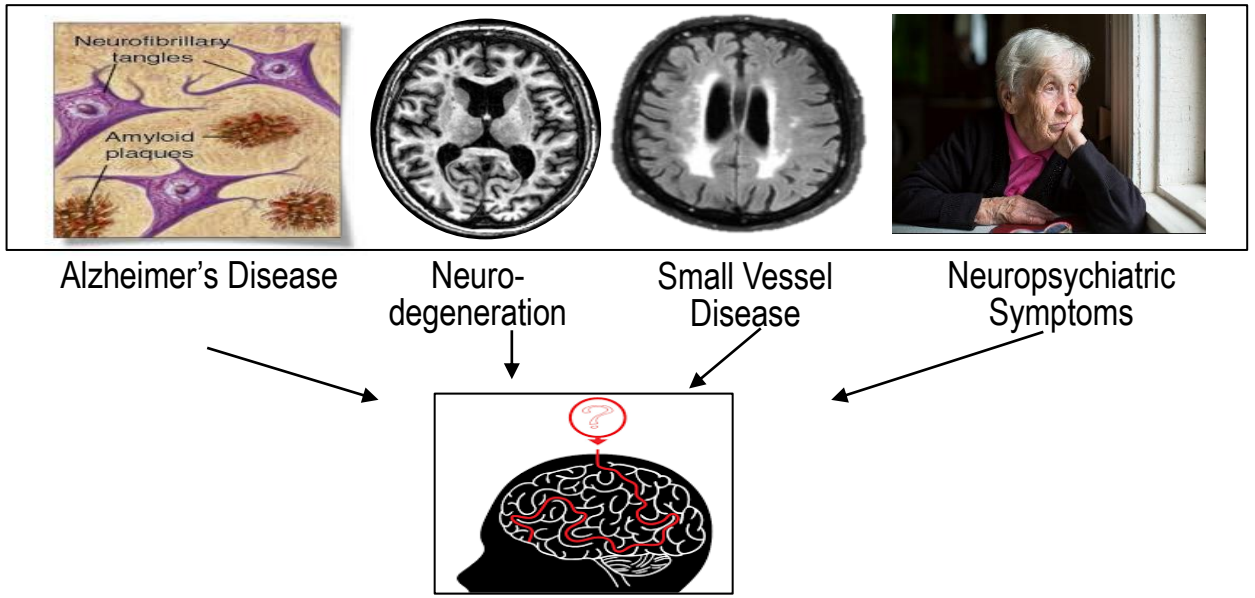
Pathological & Neuropsychiatric Pathways



Subjective Cognitive Decline Profiles

Looking Forward

Pathological & Neuropsychiatric Pathways



Subjective Cognitive Decline Profiles

- Penalized regression models (least absolute shrinkage and selection operator (LASSO)
  - Extraction of SCD items that predict specific pathways known to drive SCD → SCD profiles

Leveraging the Heterogeneity of SCD

LASSO Results: Items Selected & Weights

	SCD Item	SCD Profile	
		CSF $A\beta_{42}$ (n=45)	GDS* (n=93)
		Weight	Weight
Amyloid Profile	I fail to recognize people I know.†	-0.069	
	Change in finding my way around a familiar neighborhood.§	-0.039	
	I need a written list when I do errands to avoid forgetting things.†	-0.005	
	How often is losing the thread of thought in public speaking a problem?‡	0.006	
	How often is going to the store and forgetting what you wanted to buy a problem?‡	0.008	
Neuropsychiatric Profile	How is your memory compared to the way it was 1 year ago?‡		-0.402
	I forget steps in recipes I know well and have to look them up.†		-0.387
	I don't remember things as well as I used to.¶		-0.223
	When interrupted reading, I have trouble finding my place again.†		-0.042
	How often do directions to places present a problem?‡		-0.025
	How often does taking a test present a problem?‡		-0.016
	Change in understanding the point of what others are trying to say.§		0.007
	I forget right away what people say.†		0.018
	Change in recalling conversations a few days later.§		0.025
	Change in remembering appointments, meetings, or engagements.§		0.081
	I make mistakes in writing, typing, or operating a calculator.†		0.185
	How often do phone numbers you use frequently present a problem for you?‡		0.250
	I have trouble with my memory, paying attention, or understanding what others are saying to me.†		0.457
	Change in following a story in books or TV.§		0.477
	Do you have difficulty in remembering to turn off the stove or lights?¶		0.713
	I find it hard to keep my mind on a task/job.†		1.112

Note: analyses adjusted for age, education, and APOE-4 status; *GDS=Geriatric Depression Scale minus 4 cognitive items; ‡Memory Functioning Questionnaire, †Cognitive Difficulties Scale, §Everyday Cognition, ¶Cognitive Changes Questionnaire

Validation of Selected SCD Items & Profiles

SCD Profile	CSF $A\beta_{42}$ n=26	GDS* n=51
	R^2	R^2
Amyloid Profile	0.19	0.002
Neuropsychiatric Profile	0.03	0.20

Note: R^2 from linear regression including age, education, and *APOE*-ε4 status with fixed beta of item weights from Table 3; GDS=Geriatric Depression Scale total sore minus 4 cognitive items.

Performance of Selected SCD Items & Profiles

SCD Profile	CSF $A\beta_{42}$ n=83	GDS* n=160
	R^2	R^2
Amyloid Profile	0.13	0.10
Neuropsychiatric Profile	0.09	0.12

Note: R^2 from linear regression including age, education, and *APOE*-ε4 status with fixed beta of item weights from Table 3; GDS=Geriatric Depression Scale total sore minus 4 cognitive items.

SCD Utility in Preclinical Alzheimer's Disease Clinical Trials

How does including SCD enhance detection of amyloid positivity beyond other accessible tools?

Predictor	p-value	C-Index	Change in C-Index
MoCA*	0.44	0.75	
SCD Score	0.01	0.79	0.04
Plasma Tau	0.38	0.76	0.015
*Base model with MoCA, age, education, sex, race. Each predictor added to base model			

Participants, Collaborators, Research Team & Funding

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Vanderbilt University – Radiology
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L. Taylor Davis, MD

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T32-MH064913
UL1-TR000445 (VICTR)
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The John Hartford Foundation
Atlantic Philanthropies
American Federation for Aging Research

Vanderbilt & Aging Project (VMAP) Renewal & Expansion

Angela Jefferson

Cohort Enrollment & Follow-Up Timeline

2012 — 2016 — 2020 — 2025

Original (Legacy) Cohort (n=335)

Baseline — 18 Month — 3 Year — 5 Year

Legacy Cohort Follow-Up

7 Year — 9 Year — 11 Year

New Expansion Cohort (n=650)

Baseline — 18 Month — 3 Year

Katherine Gifford

Multiple Data Types

Demographics

Clinical History

Bloodwork

Genetics

Cardiac Imaging

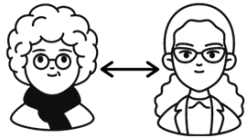
Cognitive Testing

Neuroimaging

Molecular Biomarkers

New Areas of Emphasis

Younger Age Band



Cognitively Unimpaired

Outreach & Engagement

Universal CSF Collection