Early Detection of Alzheimer's Disease

August 31, 2022

Louisiana's Health Initiative

Speaker

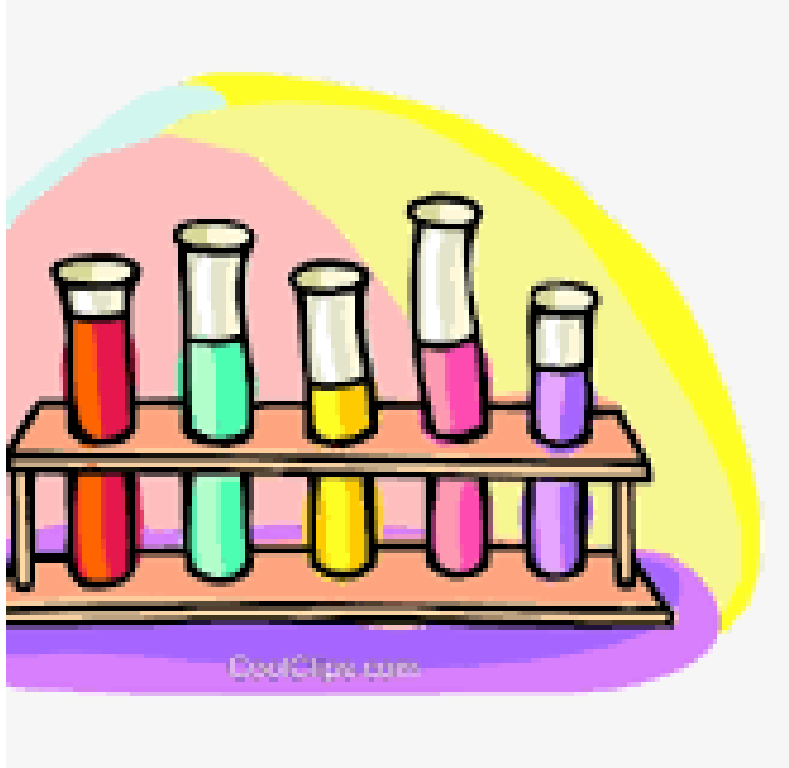
- Dr. Elizabeth Disbrow, PhD
  - Louisiana State University Shreveport Heath Sciences Center

Objectives

- To understand biomarker discovery and its clinical significance
- To review disease mechanisms as they relate to early diagnosis of Alzheimer’s disease
- To discuss emerging diagnosis tools

1. **Biomarker Background**
2. Disease Mechanism
3. Diagnosis

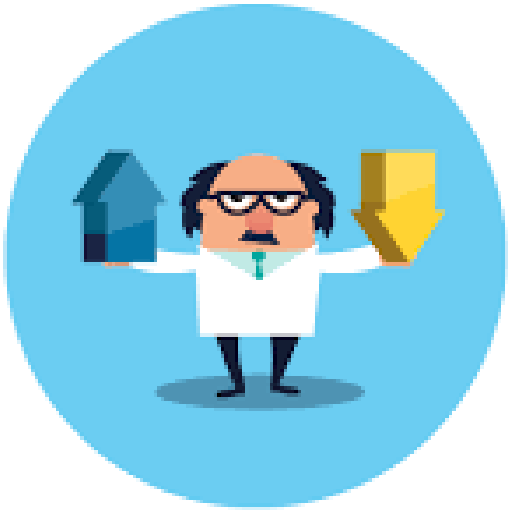
What is a Biomarker?



- a measurable substance in an organism whose presence is indicative of some phenomenon such as disease, infection, or environmental exposure.

CAN A TEST CORRECTLY IDENTIFY IF A PERSON HAS A DISEASE OR NOT?

<u>Sensitivity</u>
How well does the test identify people who have the disease?

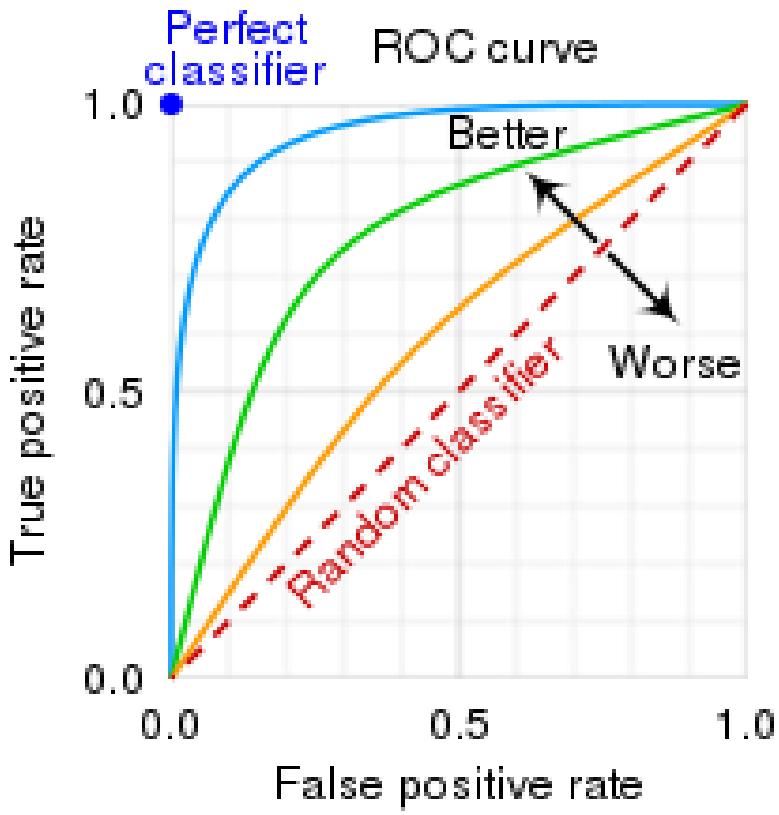


<u>Specificity</u>
How well does the test identify people who do NOT have the disease?

Sensitivity & specificity

		Test	
		Positive	Negative
True	Positive	**True Positive (Sensitivity)**	**False Negative**
	Negative	**False Positive**	**True Negative (Specificity)**

Sensitivity & specificity



Receiver Operating Characteristic (ROC) Curve

Biomarker Discovery

Phase 1: preclinical exploratory studies

- Identify leads for potentially useful biomarkers

Phase 2: clinical assay development for Alzheimer's disease pathology

- Assess ability to distinguish individuals with and without AD
- Assess variables (eg, sex, race and age) associated with biomarker status

Phase 3: longitudinal studies

- Assess the capacity of the biomarker to detect early disease and track disease progression and intervention

Phase 4: prospective diagnostic accuracy studies

- Determine the accuracy in clinic

Phase 5: disease burden reduction studies

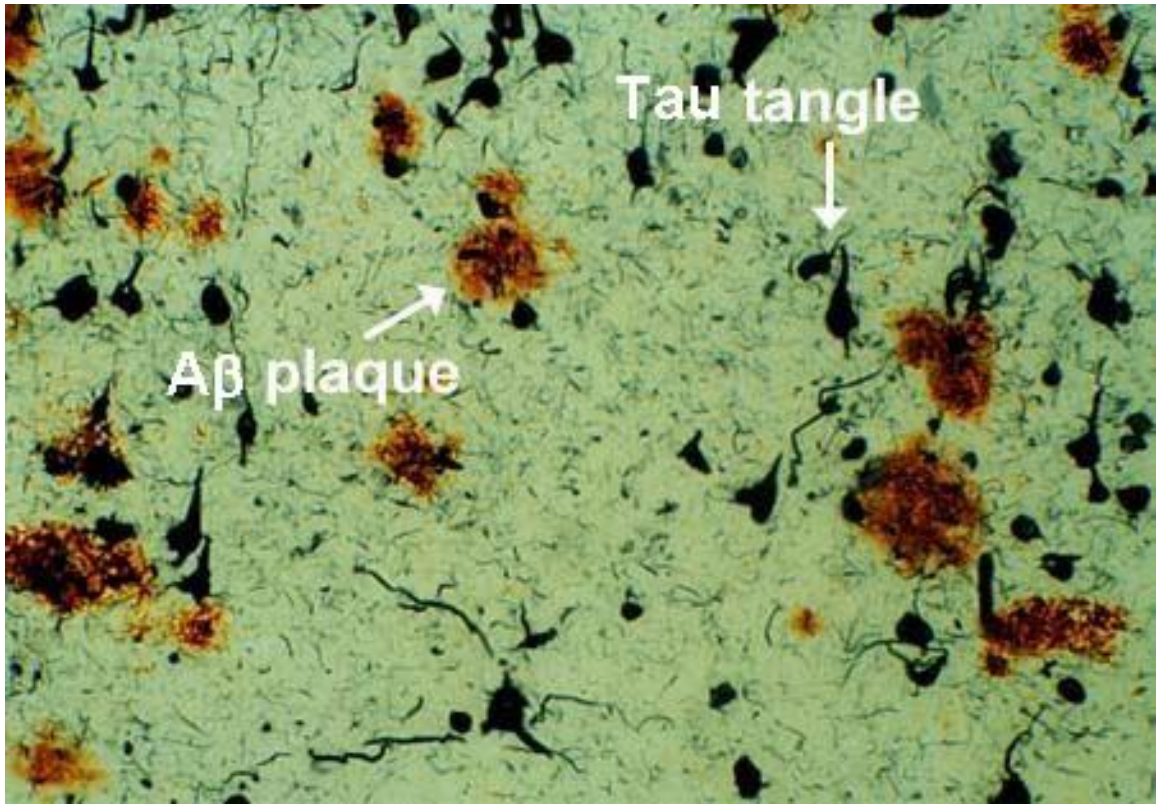
- Estimate reductions in mortality, morbidity, and disability associated with biomarker testing
- Obtain information about costs of biomarker testing and treatment and per life saved or quality-adjusted life years gained.

Adapted from Frisoni et al., 2017

1. Biomarker Background

2. **Disease Mechanism**

3. Diagnosis

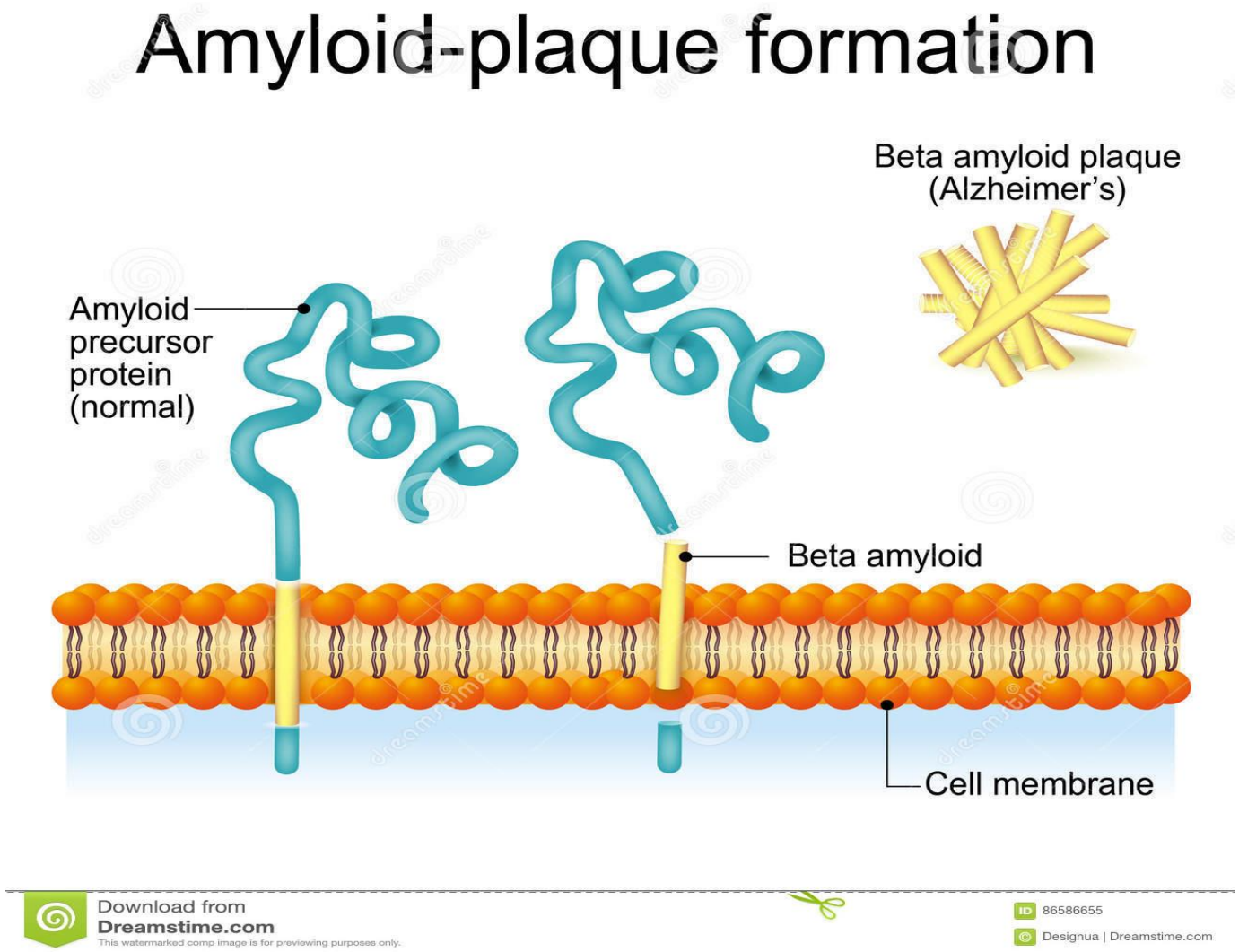


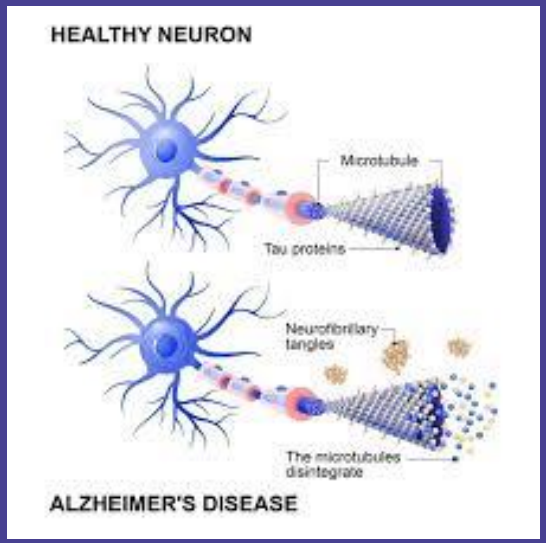
Postmortem tissue sample from an AD patient brain reveals AD pathology

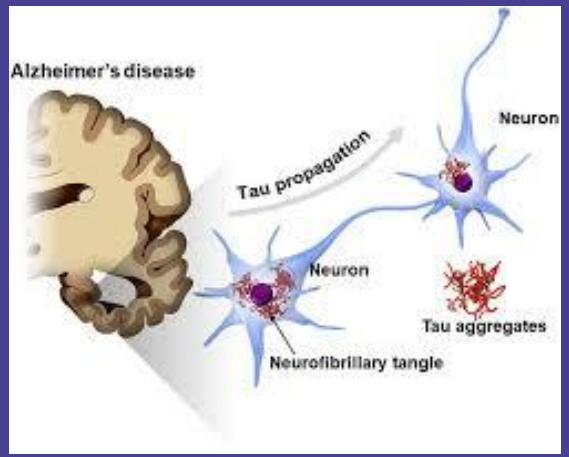
SAGE

AMYLOID PATHOLOGY

- Beta Amyloid 42, from the amyloid precursor protein, is thought to be most toxic.
- Aggregation disrupts cell to cell communication
- Aggregation activates immune cells leading to inflammation





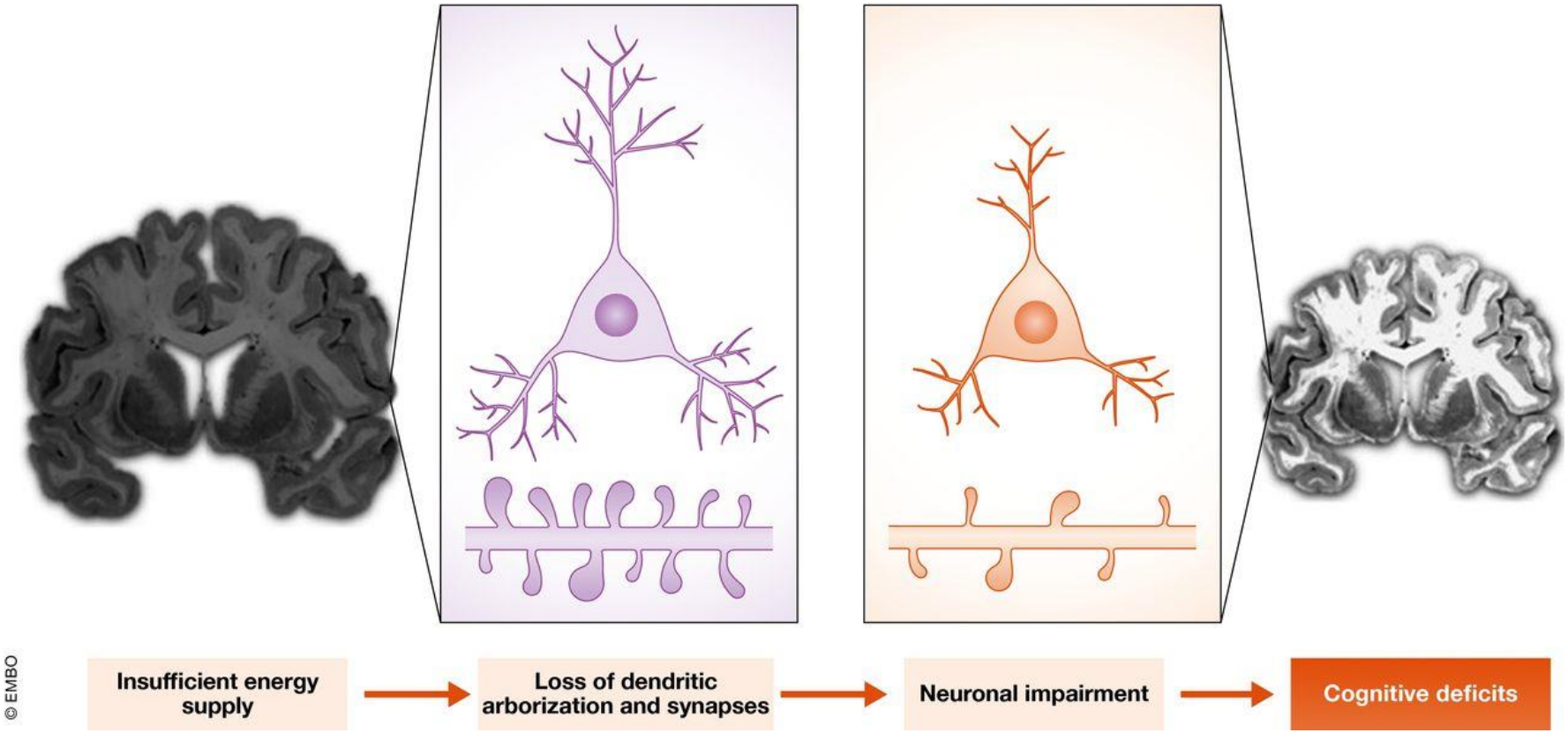


Takeda et al., 2019

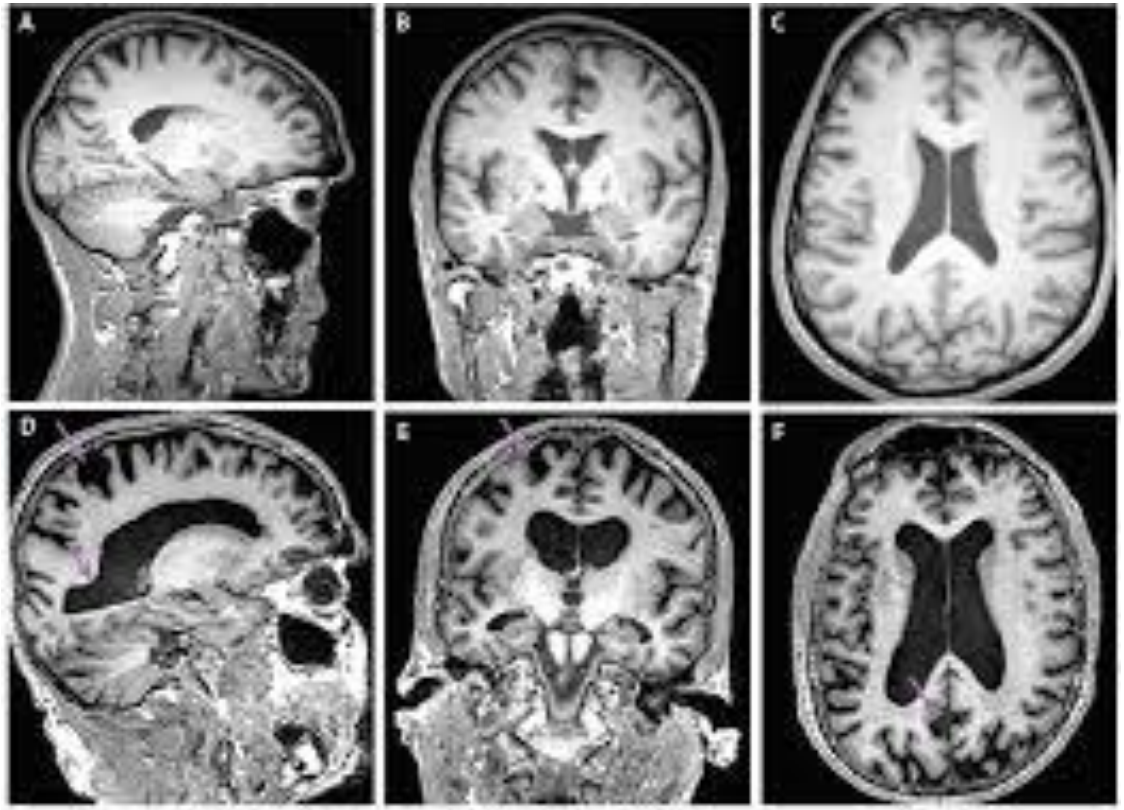
TAU PATHOLOGY

- Tau is a microtubule stabilizing protein involved in cell division and neuronal activity
- Pathological tau is released and taken up by recipient cell
- New intracellular aggregates are formed

Brain Atrophy



BRAIN ATROPHY



Amyloid, Tau & Neurodegeneration: ATN Classification

- The National Institute on Aging and Alzheimer's Association has proposed a classification system based on biomarker evidence of pathology.
- The 'ATN' classification system is used to rate people for the presence of:
  - β-amyloid (CSF Aβ or amyloid positron emission tomography (PET): 'A')
  - hyperphosphorylated τ (CSF pτ or τ PET: 'T')
  - and neurodegeneration (atrophy on structural MRI or PET, or CSF total τ: 'N')
- Other markers have already been suggested.

1. Biomarker Background

2. Disease Mechanism

3. **Diagnosis**
   - **Imaging**
   - **Blood/CSF**

How is Alzheimer’s Disease Diagnosed?

- Ask the person experiencing symptoms, as well as a family member or friend, questions about overall health, use of prescription and over-the-counter medicines, diet, past medical problems, ability to carry out daily activities, and changes in behavior and personality.
- Administer a psychiatric evaluation to determine if depression or another mental health condition is causing or contributing to a person's symptoms.
- Conduct tests of memory, problem solving, attention, counting, and language (i.e. MoCA).
- Order blood, urine, and other standard medical tests that can help identify other possible causes of the problem.
- Perform brain scans, such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET), to support an Alzheimer’s diagnosis or rule out other possible causes for symptoms.

https://www.nia.nih.gov/health/how-alzheimers-disease-diagnosed

Brain Imaging

- Positron Emission Tomography (PET) an imaging technology in which substances containing positron-emitting isotopes are introduced into the body, allowing localization of physiological processes.

- Magnetic resonance imaging (MRI) is a medical imaging technique that uses a magnetic field and computer-generated radio waves to create detailed images of the organs and tissues in your body.

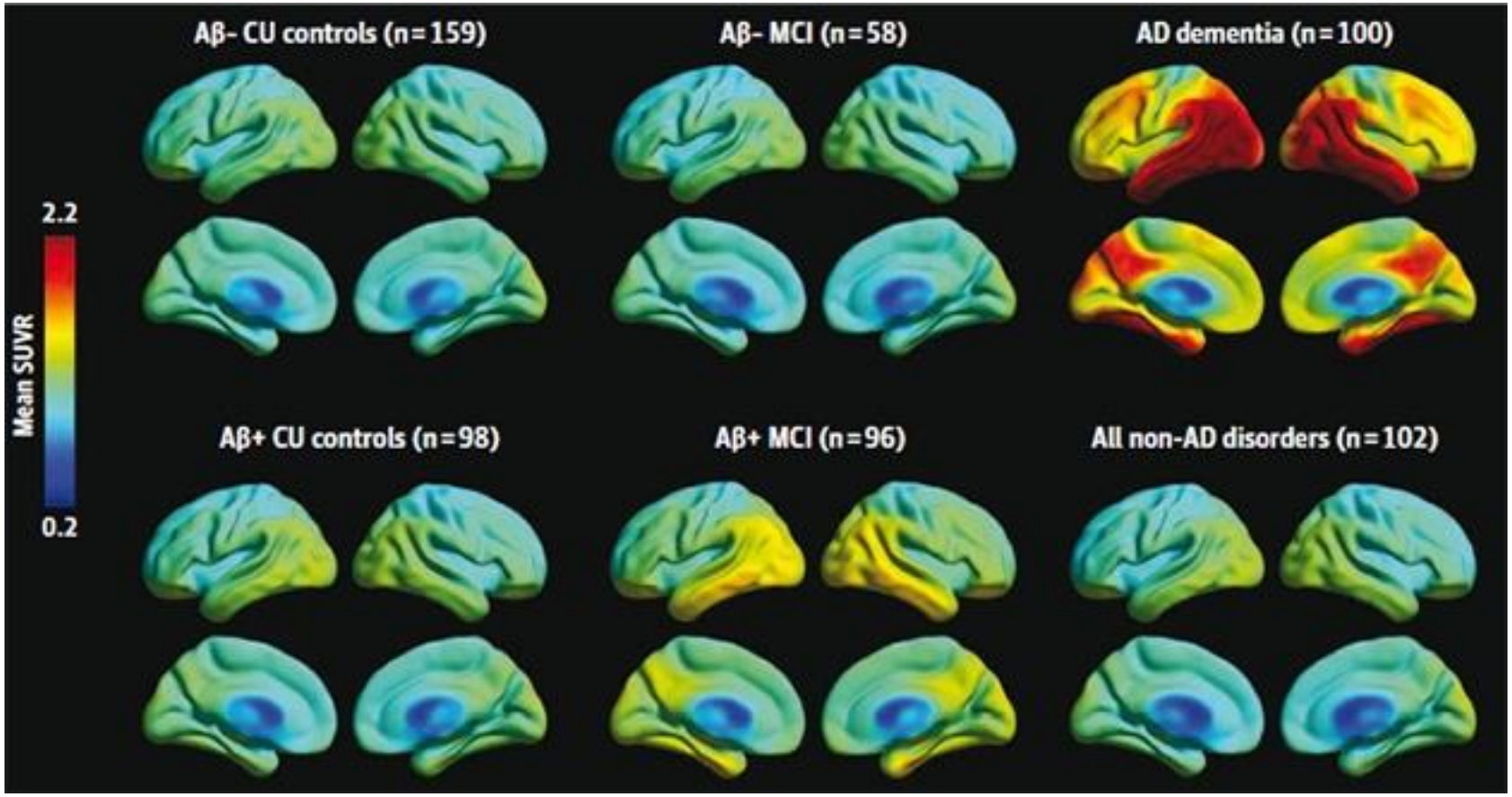
Brain Imaging

- Beta Amyloid PET - Low false negative but high false positive rate. Longitudinal data correctly classified 89% of participants who progressed to AD and 58% of participants who did not progress to AD (Amivid; Martinez et al., 2017)

- Second Generation Tau PET - identified Mild Cognitive Impairment (MCI) with an AUC of 0.80, sensitivity of 38%, and specificity of 95% (RO-948; Leuzy et al., 2020)

- New MRI model based on +/- existence of AD pathology yielded 98% accuracy. The model included data from controls and patients with FTD, PD, MCI due to Alzheimer's disease and AD. Inglese et al., 2022

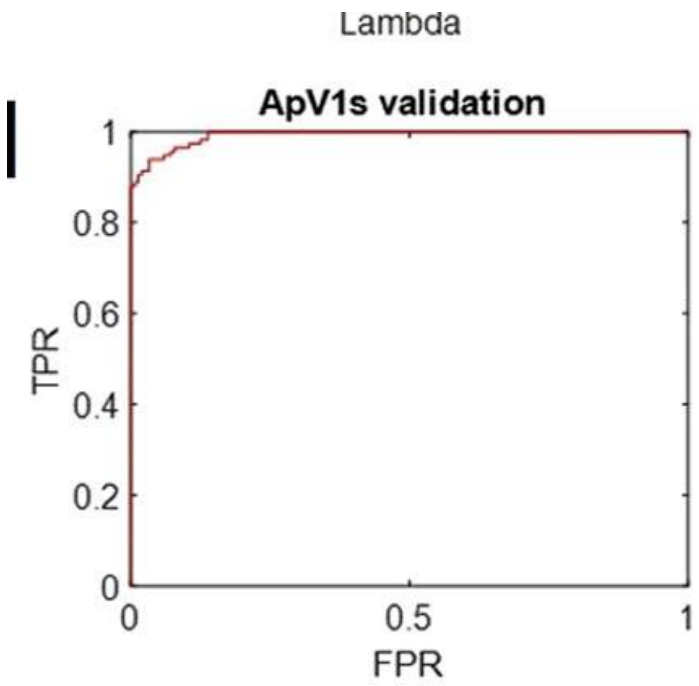
Tau RO-948 Uptake



Leuzy et al., 2020; JAMA Neurology

Brain Imaging

- New MRI model based on +/- existence of AD pathology yielded 98% accuracy. The model included data from controls and patients with FTD, PD, MCI due to Alzheimer's disease and AD. Inglese et al., 2022



Blood & CSF

- Plasma β-amyloid secondary structures had AUC of 0.80, and a specificity/sensitivity of 91% and 71% respectively, for discriminating AD patients from controls. Overall diagnostic accuracy was 86%, with the biomarker positive group being 7.9 times more likely to develop clinical AD (Nabers et al., 2018).

- CSF Aβ42/40 had an AUC of 0.93 for distinguishing AD from other disorders, and 0.91 versus healthy controls. While CSF biomarkers were highly sensitive, they lacked specificity (Leuzy et al., 2020).

Blood & CSF

- Plasma Phospho-tau217 was used to discriminate AD from other neurodegenerative diseases with an AUC of 0.89 (Palmqvist et al., *JAMA*. 2020;324(8):772-781.

New targets

Behavioral Change

BrainCheck (Braincheck.com) is a computerized cognitive testing tool. It can be used to assesses a wide range of cognitive domains, including reaction time, immediate and delayed recall, processing, speed executive function, visual attention, task switching, and coordination in about 15 min.

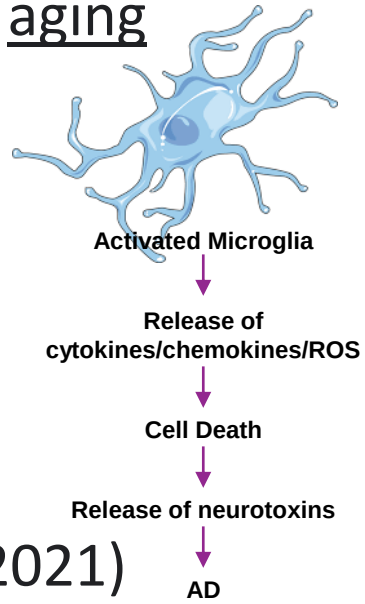
BrainCheck Overall Scores

- 88% sensitivity/specificity for separating the Control from Dementia group
- 77% sensitivity/specificity in separating the Mild Cognitive Impairment group from Control and Dementia groups (Sun et al., 2021)

New targets

Neuroinflammation

- The brain's innate immune system is triggered following an inflammatory challenge such as those posed by injury, infection, exposure to a toxin, neurodegenerative disease, or aging
- The accumulation of amyloid fibrils causes tissue **damage** and elicits immune cell infiltration into tissue and proinflammatory cytokine production
- PET imaging of microglia activation and triggering receptors showed a correlation with cognitive dys-function and protein accumulation (Pascoal et al., 2021)



New targets

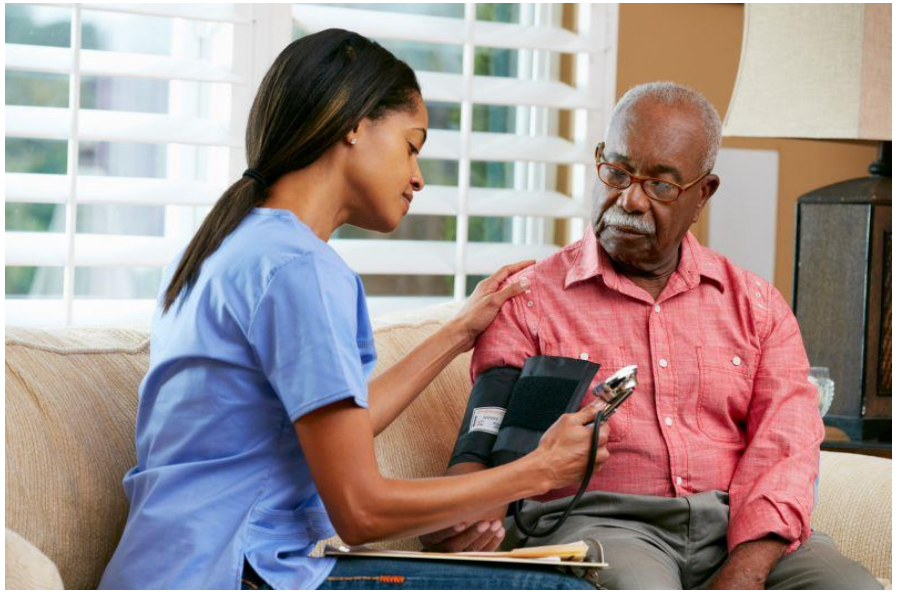
Mitochondrial Function

- Mitochondria are the energy powerhouse of the cell
- New PET tracer targeting mitochondrial function showed decreased metabolism and energy production in medial temporal cortex in AD (Terada et al., 2020)
- Peripheral biomarker discovery is in early stages (Bell et al., 2021)

New targets

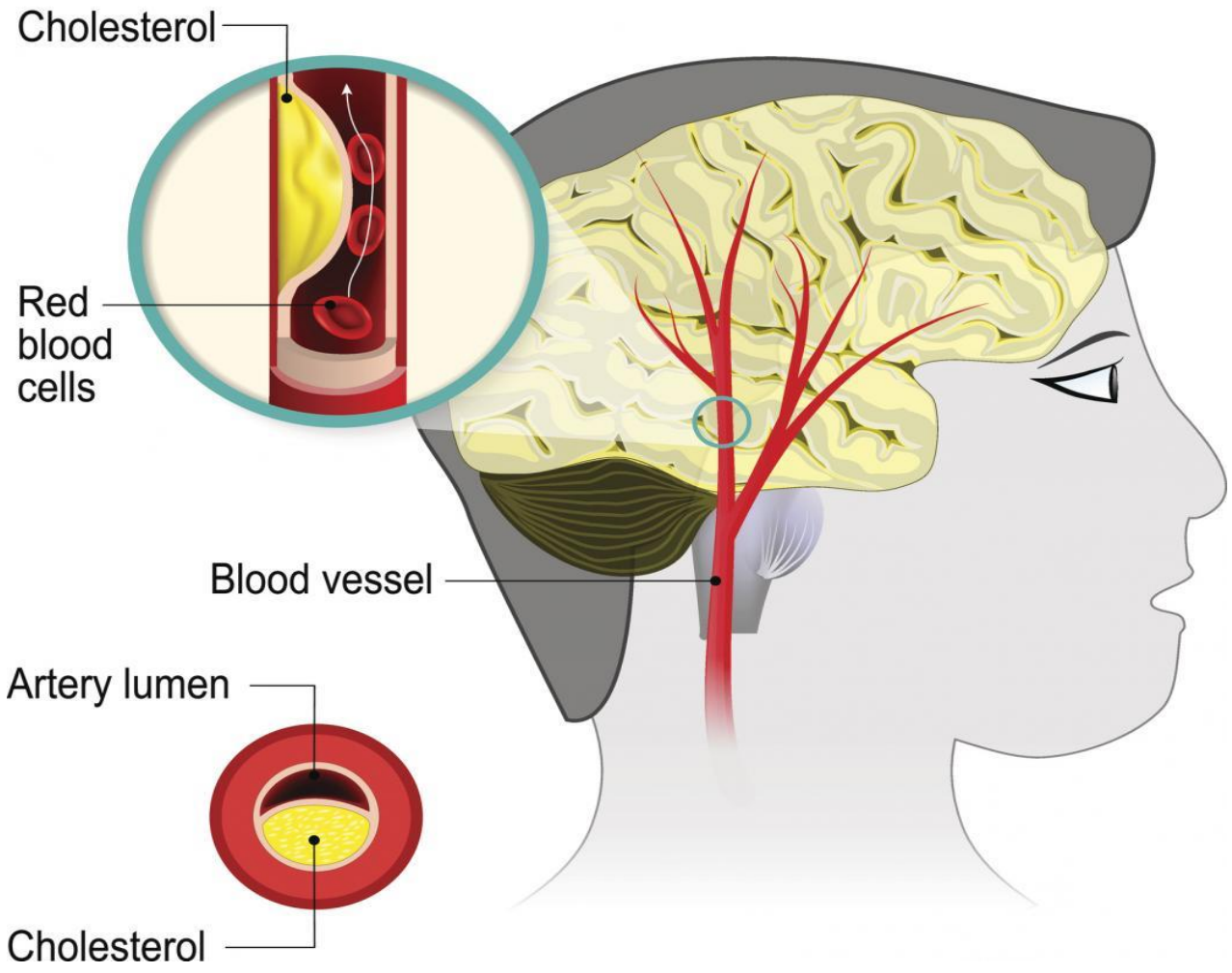
Vascular Dysregulation Hypothesis

Imbalance between blood flow-based substrate delivery and brain energy requirements intensify common cardiovascular risks for dementia

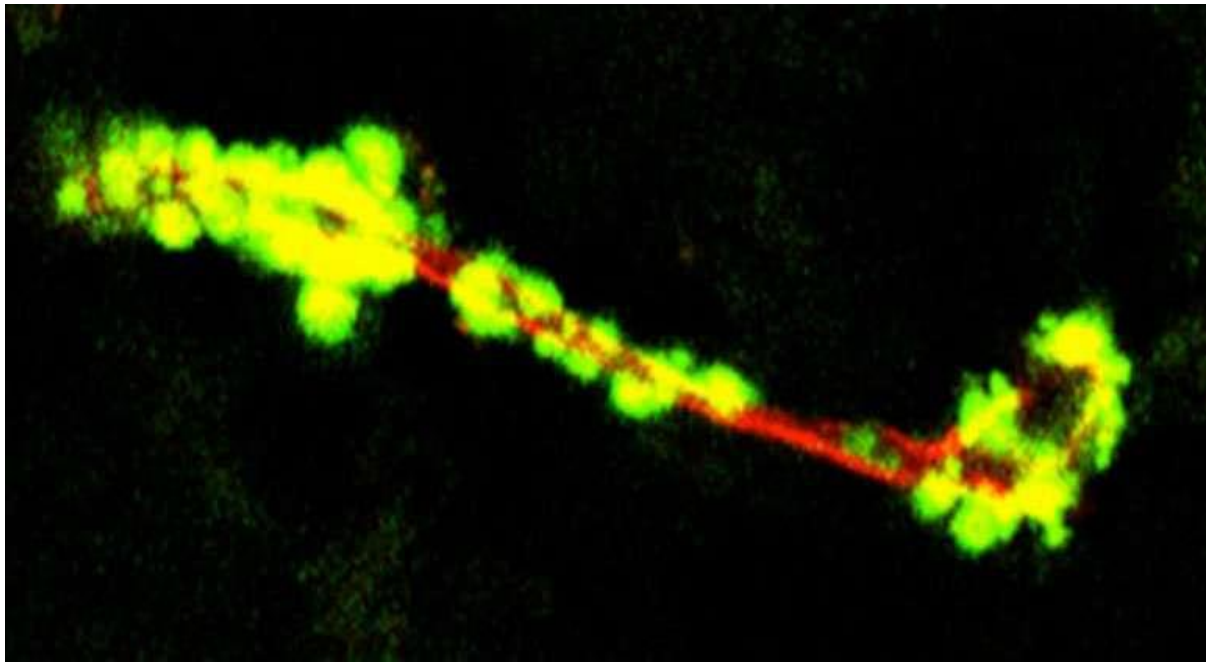


- Longitudinal data indicates that persons with a history of high blood pressure or cholesterol are twice as likely to get Alzheimer's disease. Those with both are four times as likely to become demented.
- Heart disease risk factors in midlife such as diabetes, elevated blood pressure, and smoking cigarettes—are associated with an increased risk for dementia.
- If cerebrovascular disease is present, it takes fewer plaques and tangles to produce the same degree of dementia.

ATHEROSCLEROSIS



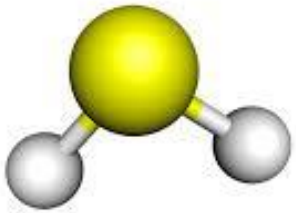
Brain Blood Vessel Amyloid



Brain blood vessel amyloid could promote different pathological responses, i.e., inflammation, which likely contributes differently to cognitive impairment and dementia than neuron amyloid.

Plasma Hydrogen Sulfide: A Novel Biomarker of Cognitive Function in Alzheimer's Disease and Related Dementias

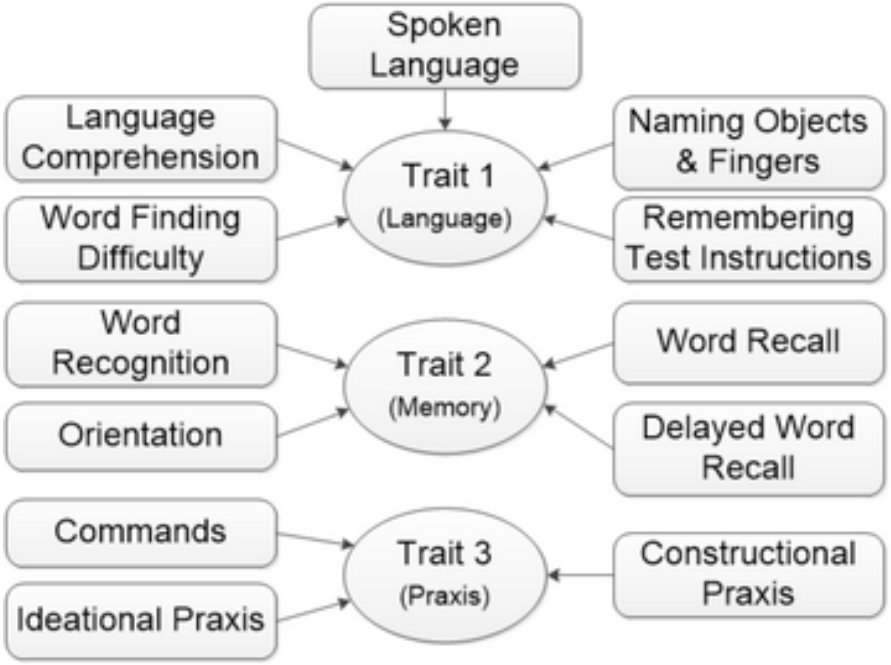
Elizabeth Disbrow, Karen Y. Stokes, Christina Ledbetter, James Patterson, Roger E. Kelley, Tyler Reekes, Lana Larmeu, Vinita Batra, Shuai Yuan, Urska Cvek, Marjan Trutschl, Phillip Kilgore, J. Steven Alexander, Christopher G. Kevil



Hydrogen sulfide (H_2S) acts as a gaseous signaling molecule and chemical reagent involved in many physiological processes, including the pathogeneses of neurodegenerative disease, heart failure, and diabetes.

While metabolic indicators of cardiovascular disease may contribute to ADRD pathogenesis, relationships between blood-borne sulfide species and clinical cognitive dysfunction are understudied.

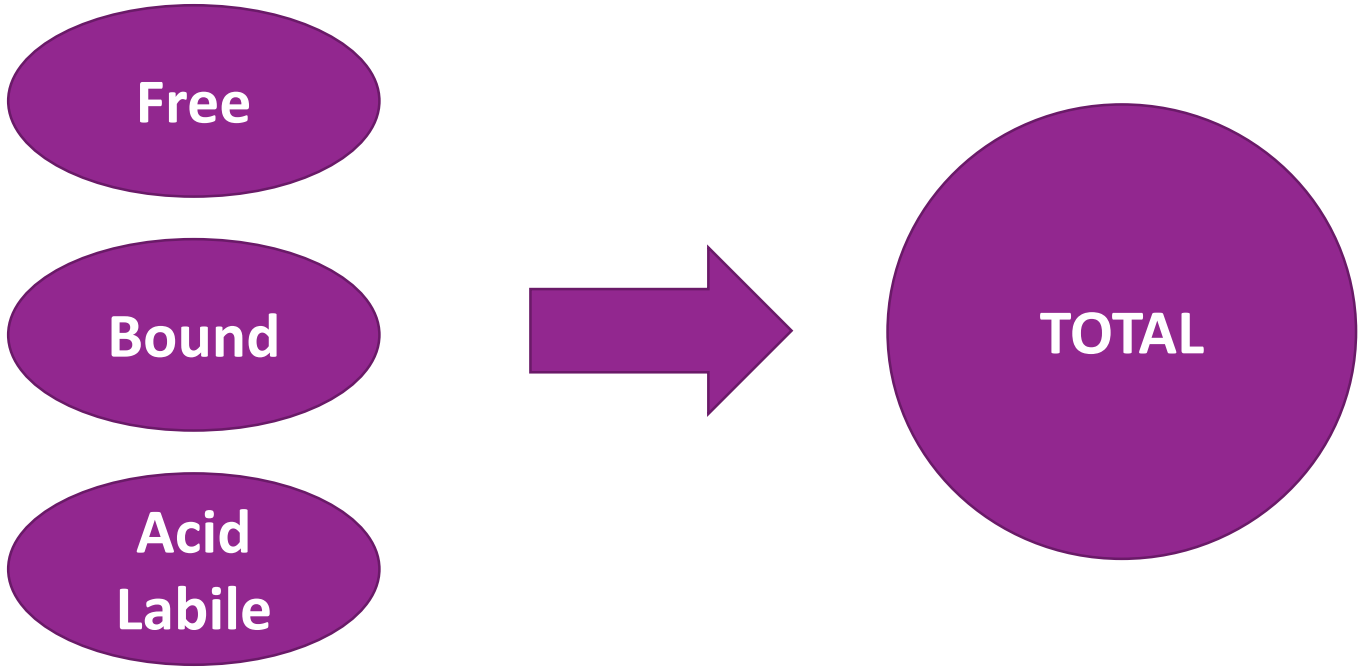
Neuropsychological Assessment



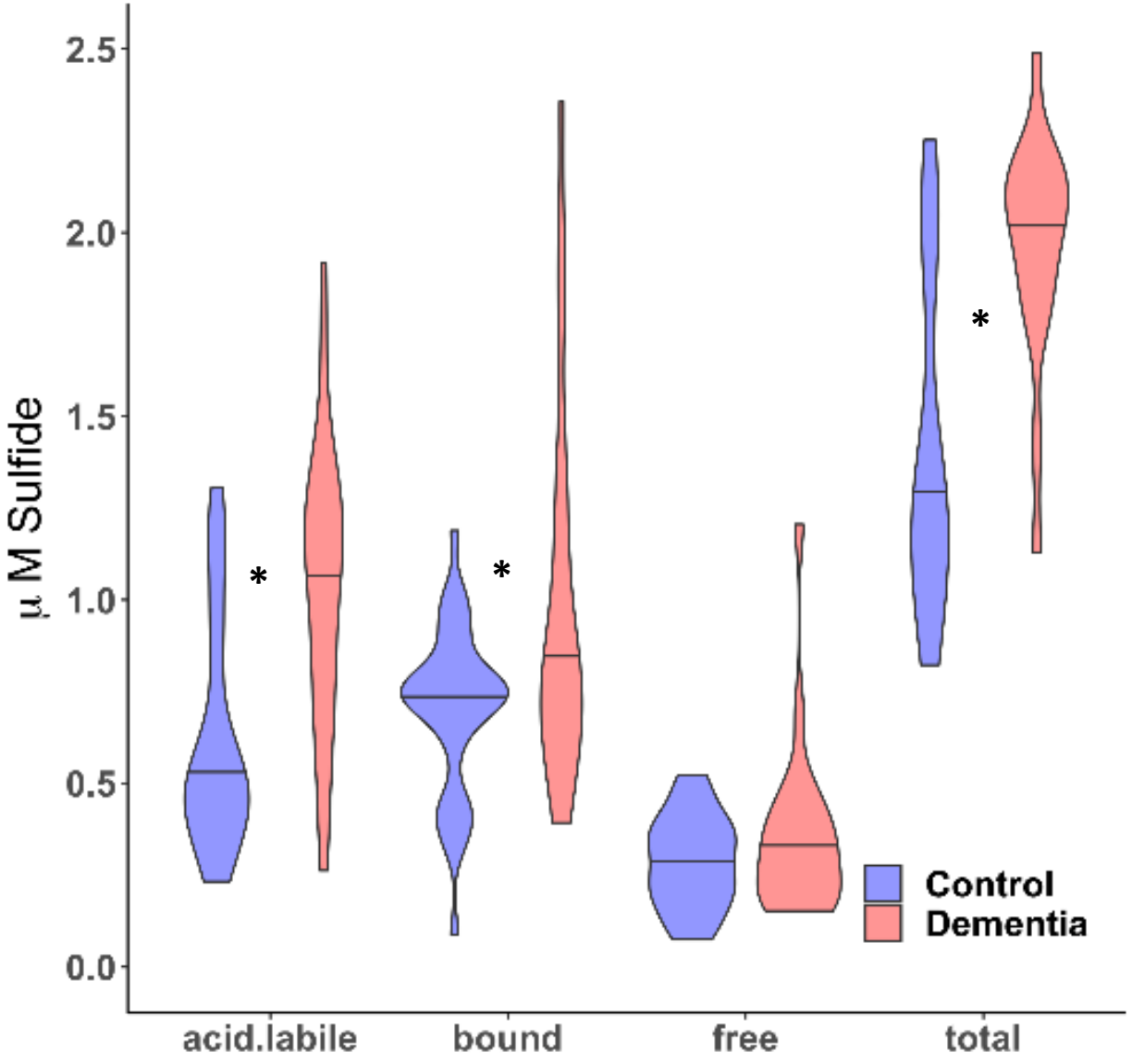
- **<u>Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)</u>** is a set of tasks used to measures memory and other cognitive functions
- Total scores range from 0 to 70
- Higher scores (≥17) indicate greater cognitive impairment

HYDROGEN SULFIDE METABOLISM

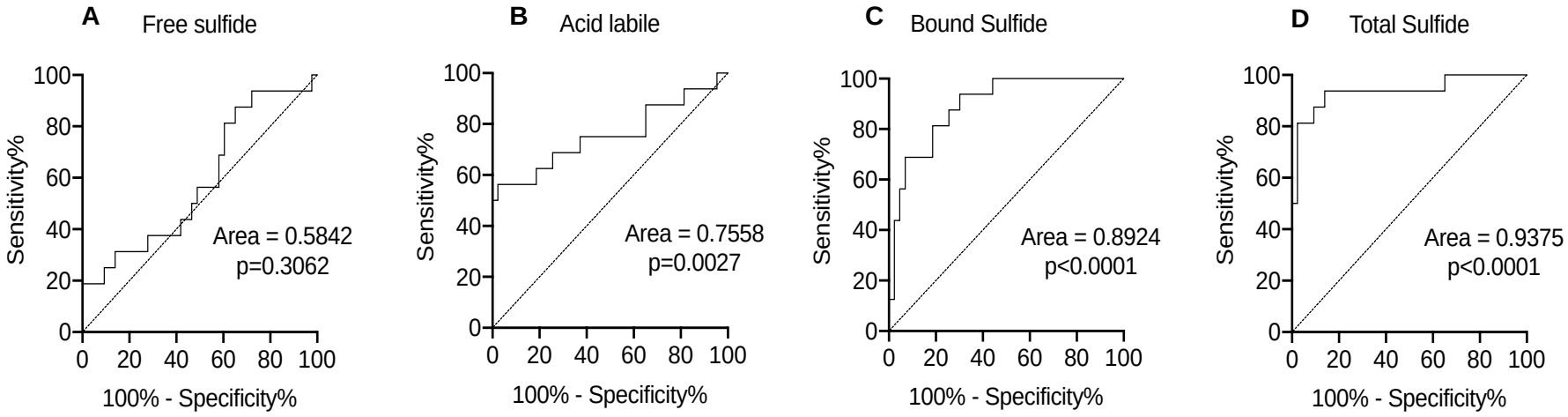
- Sulfides Exist in Several Forms



Levels of Sulfide Metabolites are Elevated in AD



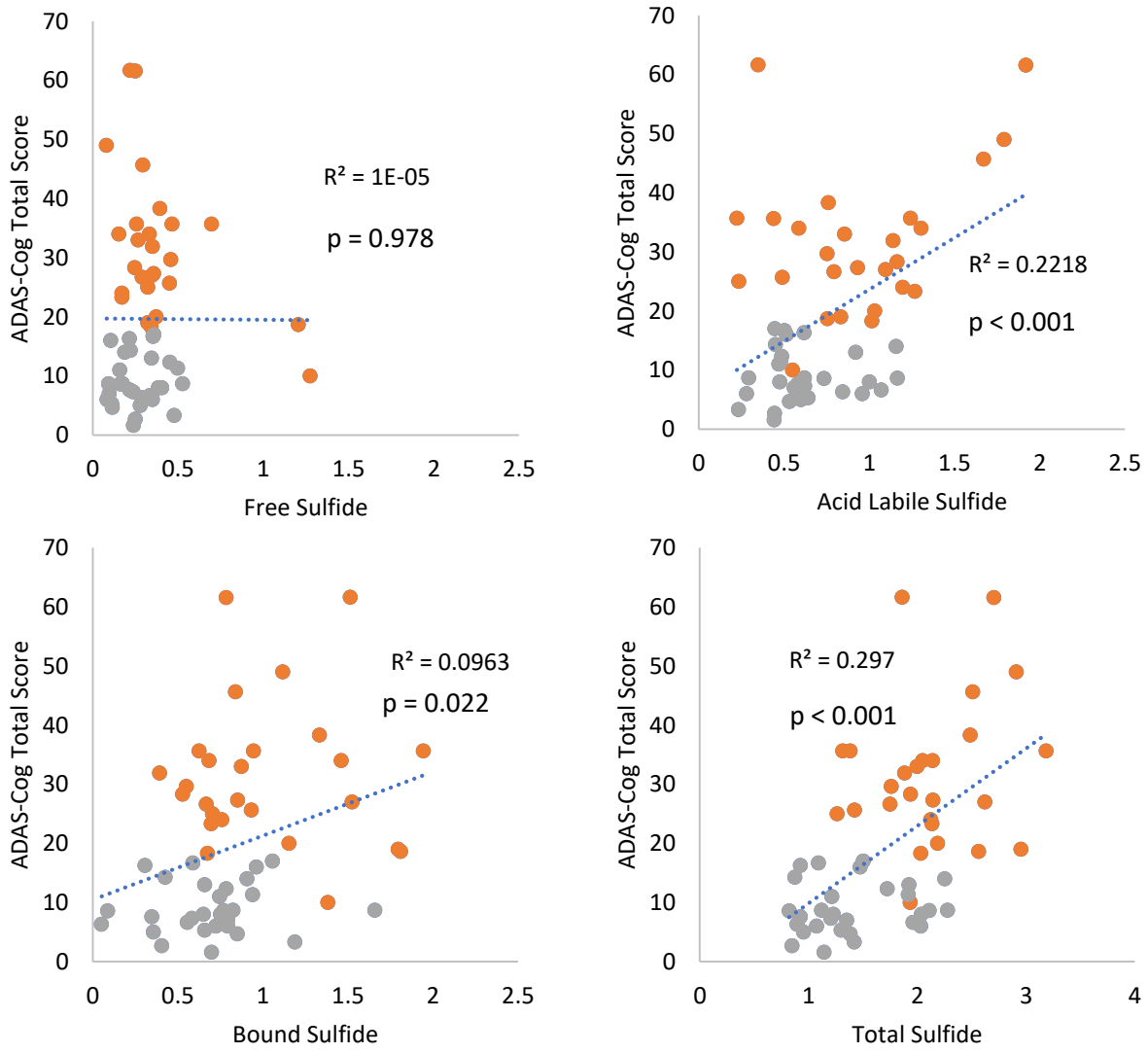
Receiver-operating characteristic (ROC) curve analyses demonstrate that sulfides are indicators of ADRD



ROC curve analysis results for total sulfide:

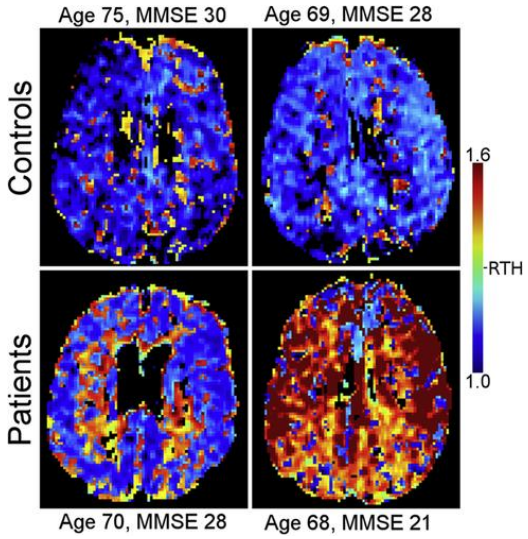
AOC=0.94, sensitivity of 0.89 and specificity of 0.98

Sulfide Metabolites Correlate with Cognitive Function



Control ADRD

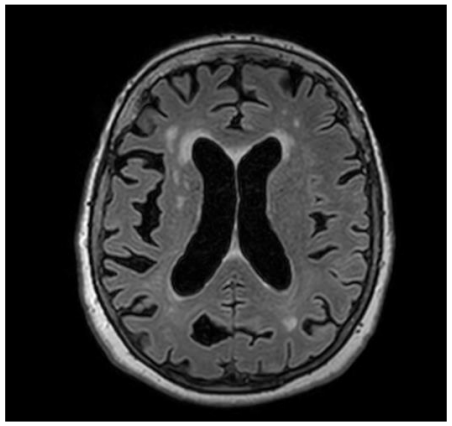
Sulfide Metabolites Correlate with Cerebrovascular Impairment

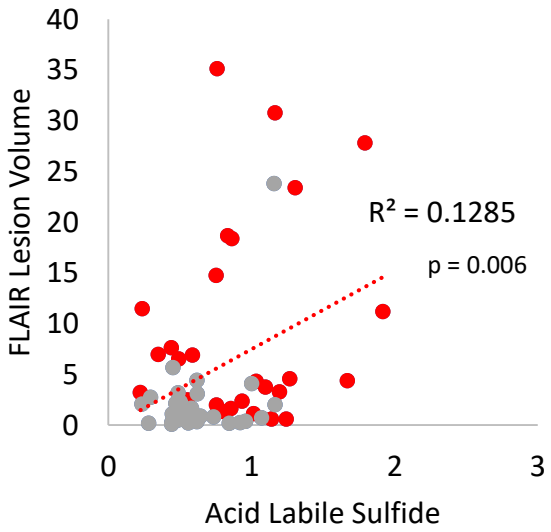


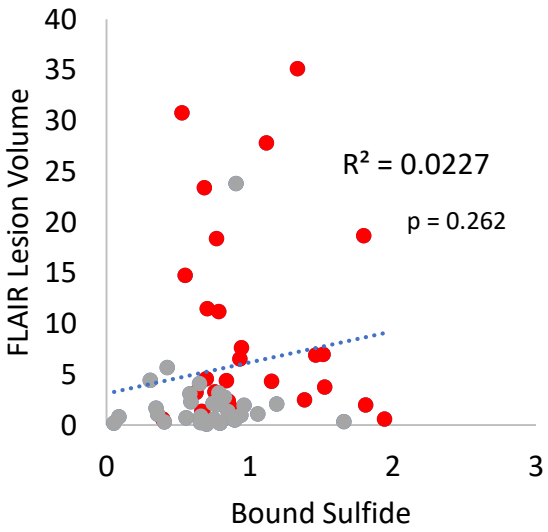
Hachinski et al. 2019

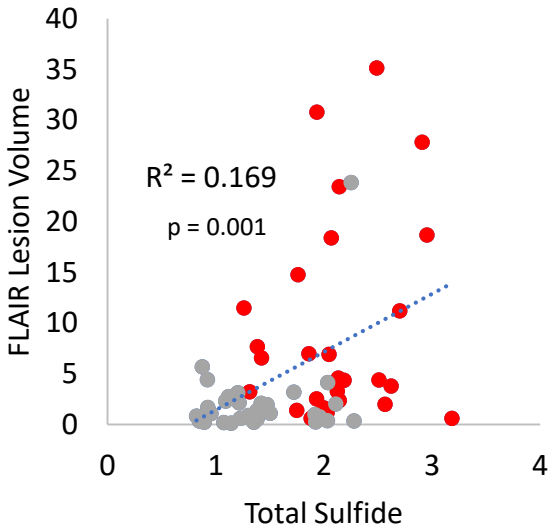
Brains of Alzheimer's Disease patients exhibit capillary hypoperfusion

FLAIR



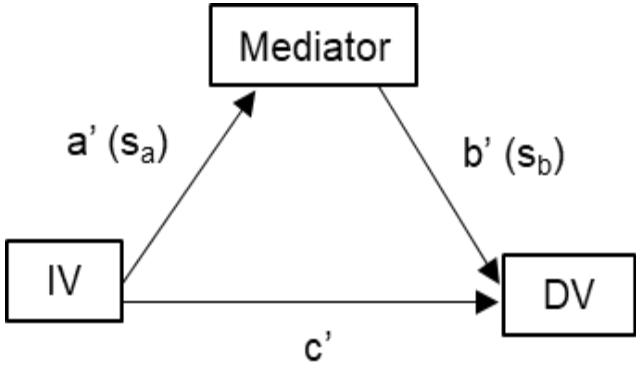




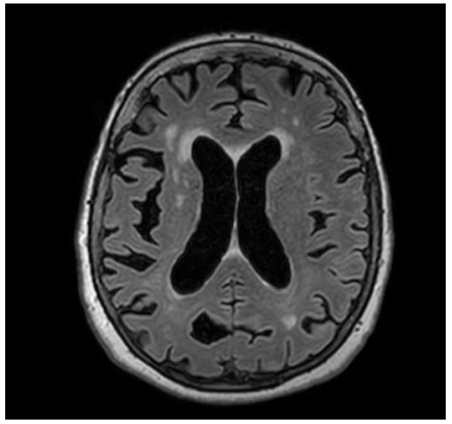


Control ADRD

Sulfide Metabolites Mediate The Relationship Between Cerebrovascular Impairment & Cognitive Dysfunction

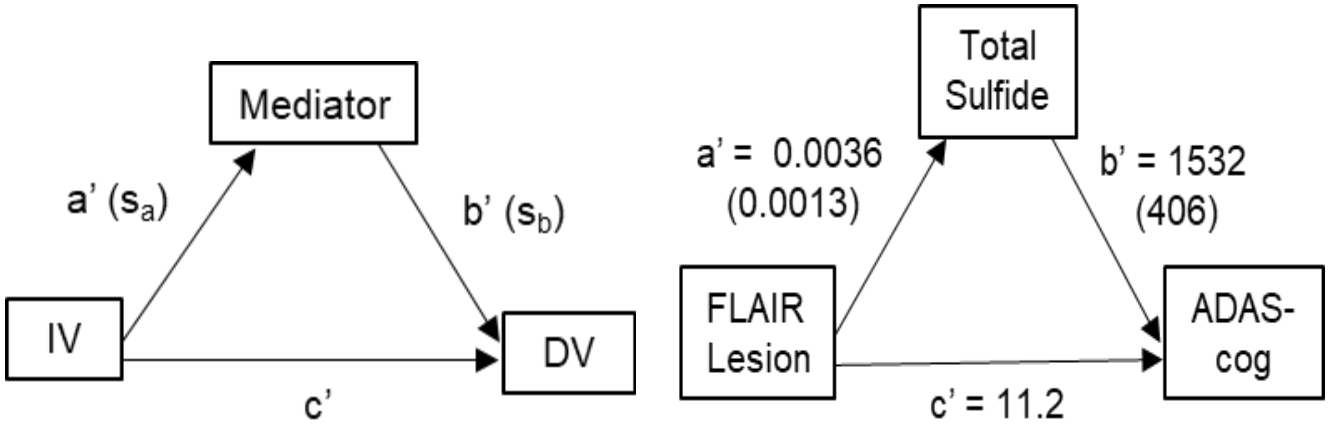


FLAIR

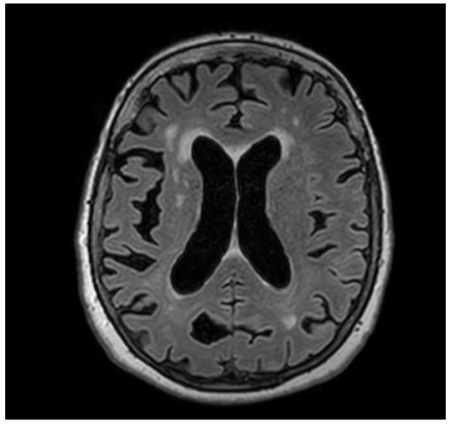


Disbrow E, Stokes KY, Ledbetter C, Patterson J, Kelley R, Pardue S, Reekes T, Larmeu L, Batra V, Yuan S, Cvek U, Trutschl M, Kilgore P, Alexander JS, Kevil CG. Plasma hydrogen sulfide: A biomarker of Alzheimer's disease and related dementias. Alzheimers Dement. 2021 Aug;17(8):1391-1402. doi: 10.1002/alz.12305. Epub 2021 Mar 12. PMID: 33710769; PMCID: PMC8451930.

Sulfide Metabolites Mediate The Relationship Between Cerebrovascular Impairment & Cognitive Dysfunction

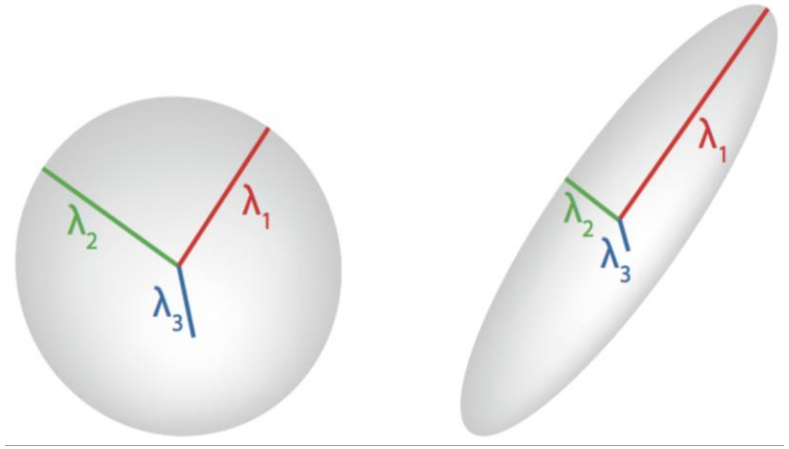


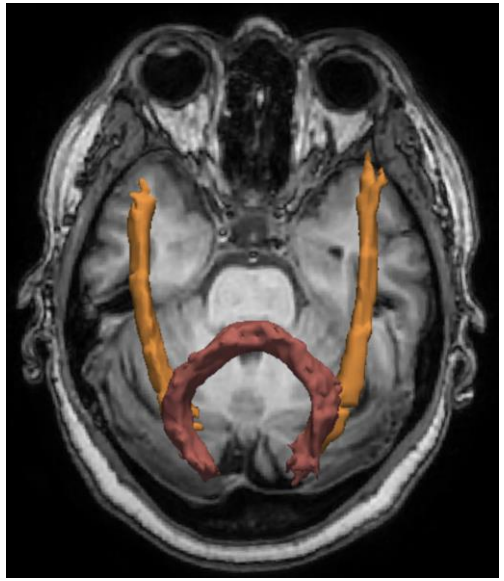
FLAIR



Disbrow E, Stokes KY, Ledbetter C, Patterson J, Kelley R, Pardue S, Reekes T, Larmeu L, Batra V, Yuan S, Cvek U, Trutschl M, Kilgore P, Alexander JS, Kevil CG. Plasma hydrogen sulfide: A biomarker of Alzheimer's disease and related dementias. Alzheimers Dement. 2021 Aug;17(8):1391-1402. doi: 10.1002/alz.12305. Epub 2021 Mar 12. PMID: 33710769; PMCID: PMC8451930.

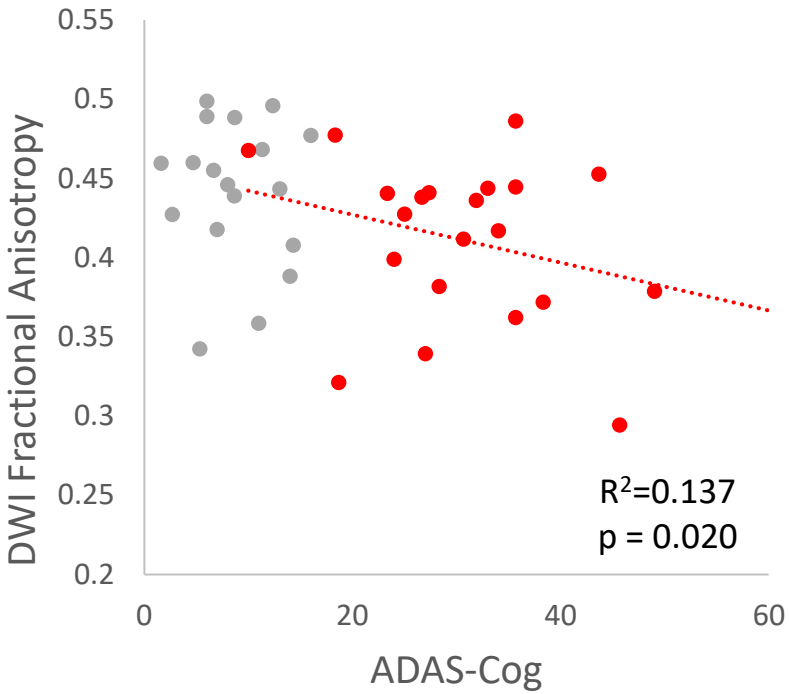
Diffusion Weighted MRI

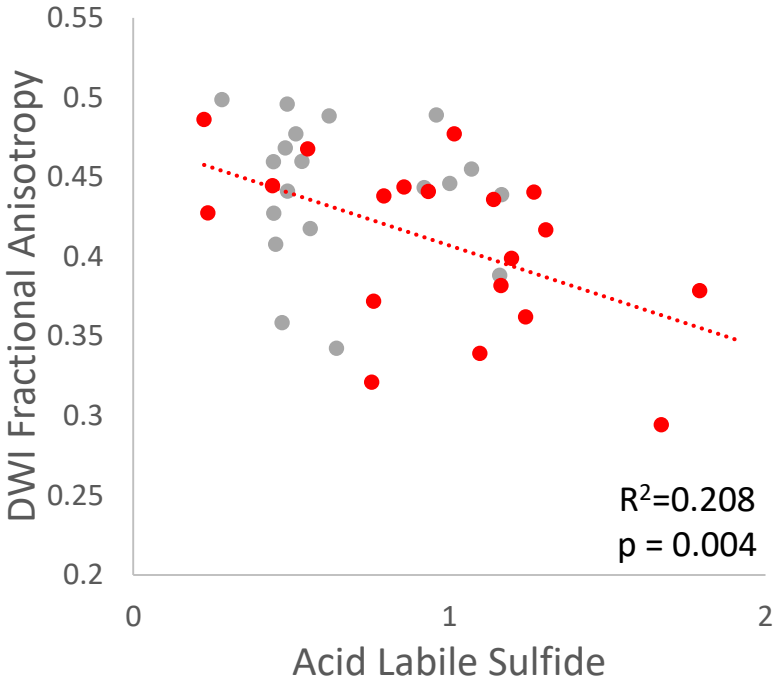




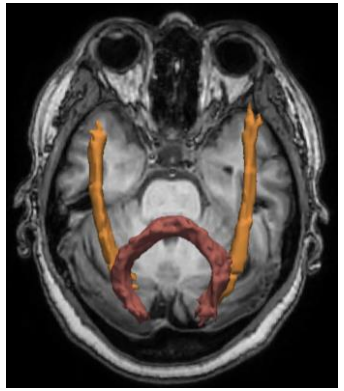
Diffusion images were processed and quantified using the TRActs Constrained by UnderLying Anatomy (TRACULA) pipeline suite of the FreeSurfer software package version 6.0. TRACULA provides probabilistic reconstructions and standard diffusion measures including axial, radial and mean diffusivities and fractional anisotropy for 18 white matter pathways.

Inferior Longitudinal Fasciculus Fractional Anisotropy



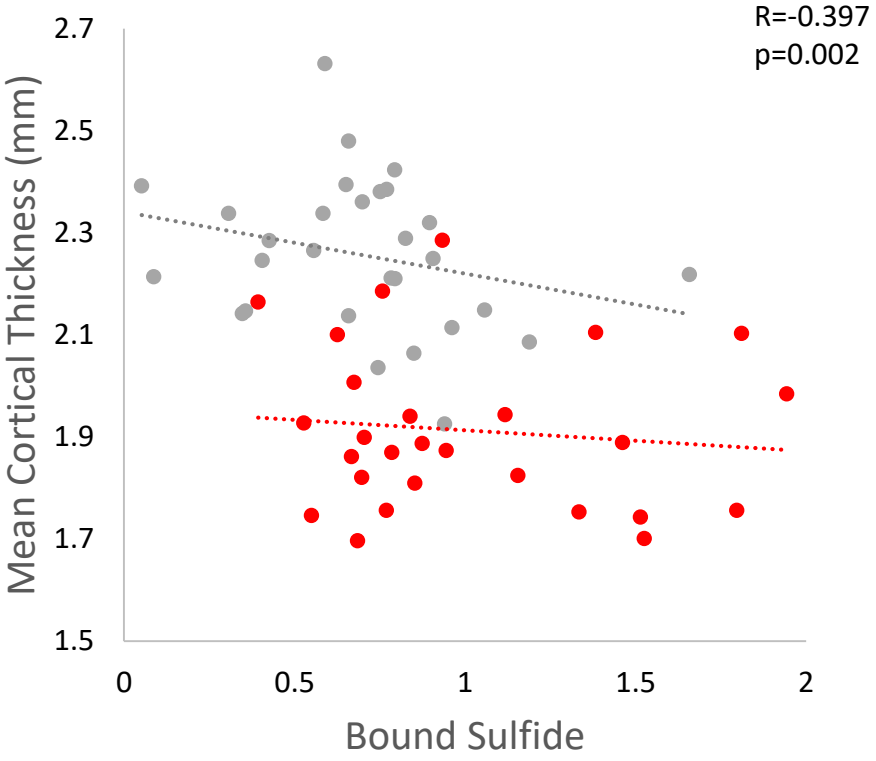


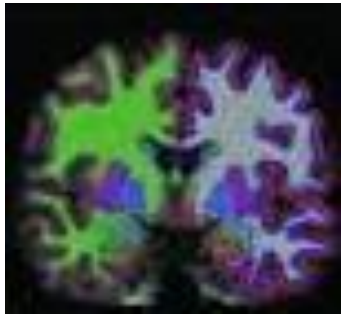
Decreased fractional anisotropy in the inferior longitudinal fasciculus is significantly associated with both increased acid labile sulfide and poorer cognitive performance.



Control ADRD

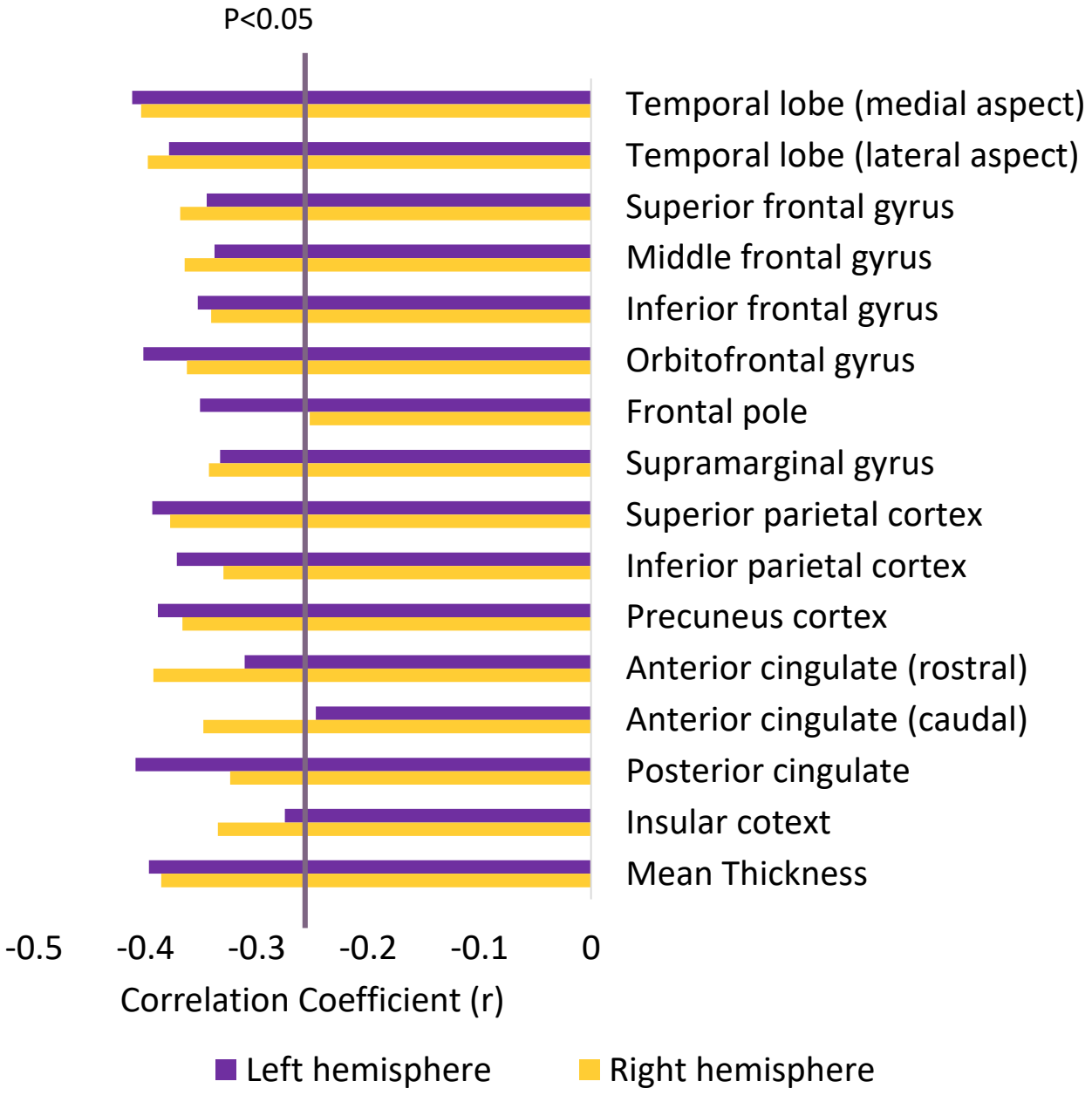
Cortical Thickness is Correlated with Bound Sulfide



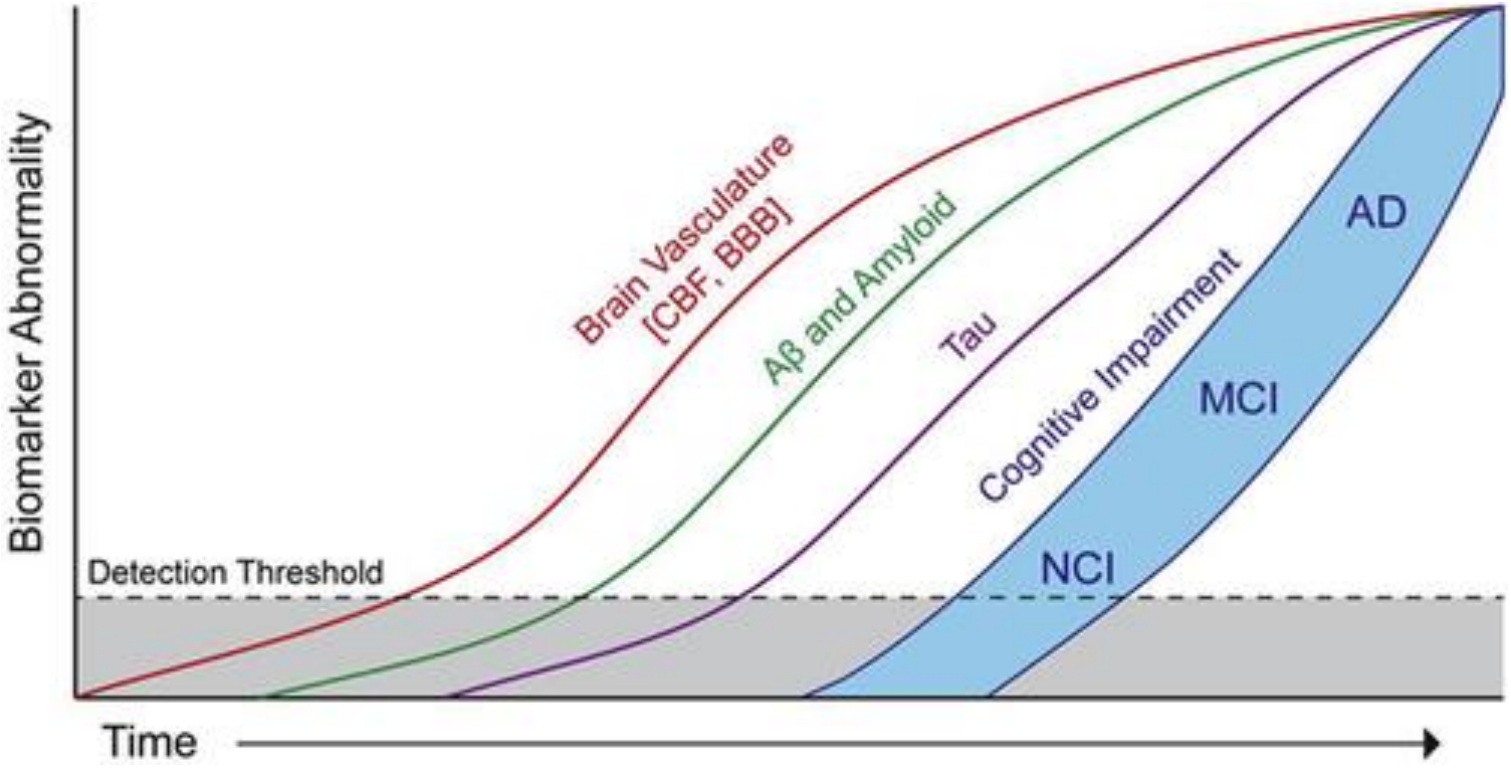


Control ADRD

Bound Sulfide Correlates with Cortical Thickness



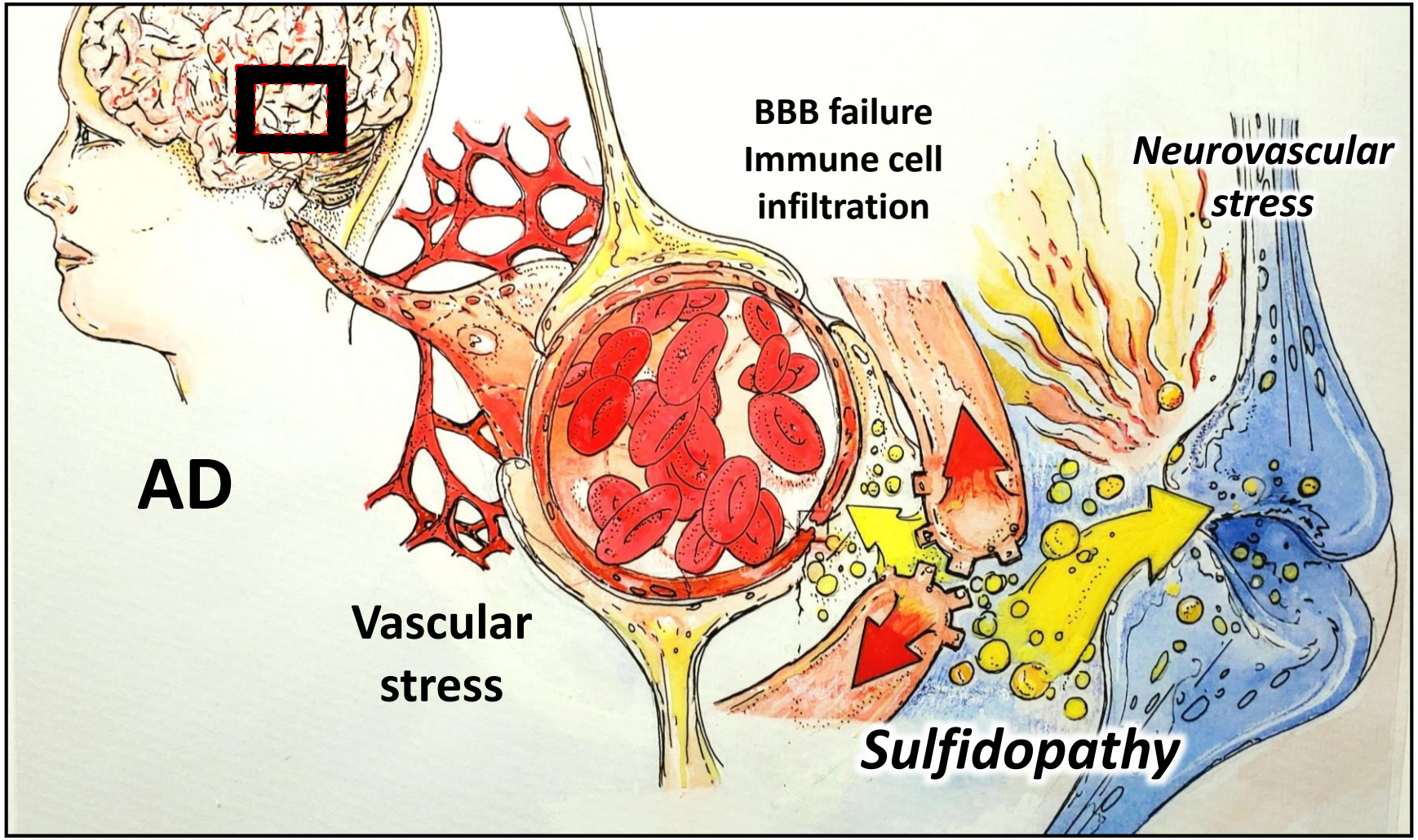
The “Vascular Hypothesis” of Alzheimer’s Disease



Alzheimers Dement. 2019 Jul;15(7):961-984

We recently showed that in ADRD, dementia-associated microvascular disease and cognitive dysfunction were linked with redox-related *disturbances in sulfide metabolism*.

Disbrow E, Stokes KY, Ledbetter C, Patterson J, Kelley R, Pardue S, Reekes T, Larmeu L, Batra V, Yuan S, Cvek U, Trutschl M, Kilgore P, Alexander JS, Kevil CG. Plasma hydrogen sulfide: A biomarker of Alzheimer's disease and related dementias. Alzheimers Dement. 2021 Aug;17(8):1391-1402. doi: 10.1002/alz.12305. Epub 2021 Mar 12. PMID: 33710769; PMCID: PMC8451930.



Sulfides Mediate Vascular Dysfunction Leading to AD
'Neurovascular Sulfidopathy'

Disbrow E, Stokes KY, Ledbetter C, Patterson J, Kelley R, Pardue S, Reekes T, Larmeu L, Batra V, Yuan S, Cvek U, Trutschl M, Kilgore P, Alexander JS, Kevil CG. Plasma hydrogen sulfide: A biomarker of Alzheimer's disease and related dementias. Alzheimers Dement. 2021 Aug;17(8):1391-1402. doi: 10.1002/alz.12305. Epub 2021 Mar 12. PMID: 33710769; PMCID: PMC8451930.

The Bridge: 851 Olive St.
(318) 656-4800

- Support Groups
- Social Activates
- Access to Care
- Education
- Counseling
- Clinical Trials

SECOND SATURDAY FOR SENIORS
HOSTED BY
THE BRIDGE ALZHEIMER'S AND DEMENTIA RESOURCE CENTER
&
LSU HEALTH SHREVEPORT CENTER FOR BRAIN HEALTH

GAME DAY

BINGO! GAMES! PRIZES!
EVERYONE WELCOME!

MARCH 9, 2022
10AM–12PM
BROADMOOR PRESBYTERIAN

1915 Grover Place Shreveport, LA 71105

SECOND SATURDAY FOR SENIORS
HOSTED BY
THE BRIDGE ALZHEIMER'S AND DEMENTIA RESOURCE CENTER
&
LSU HEALTH SHREVEPORT CENTER FOR BRAIN HEALTH

LET'S DANCE!

Senior Exercise and Chair Aerobics
Boogie to the Oldies
EVERYONE WELCOME!

APRIL 9, 2022
10AM–12PM
BROADMOOR PRESBYTERIAN

1915 Grover Place Shreveport, LA 71105

SECOND SATURDAY FOR SENIORS
HOSTED BY
THE BRIDGE ALZHEIMER'S AND DEMENTIA RESOURCE CENTER
&
LSU HEALTH SHREVEPORT CENTER FOR BRAIN HEALTH

FOOD FOR THOUGHT

Healthy eating tips & tricks by Shreveport Green
Plus a surprise to take home!

JUNE 11, 2022
10AM–12PM
BROADMOOR PRESBYTERIAN

1915 Grover Place Shreveport, LA 71105

Acknowledgements

Team

Tyler Reekes
Christina Ledbetter
Sibile Pardue
Vinita Batra
Shuai Yuan
Mansoureh Barzegar, Ph.D.
Shantel Vital, M.S.
Winny Yun, Ph.D.
Megan Butler, M.S.

Collaborators

James Patterson, MD
Roger Kelley, MD

LSU-Shreveport
Urska Cvek, Sci.D., M.B.A.
Marjan Trutschl, Sci.D., M.B.A.
Phillip Kilgore

Pennington
Ron Horswell, Ph.D.

Funding:
P20 GM121307, NIH/NIGMS

QUESTIONS?

Contact Information

- Dr. Elizabeth Disbrow
  - elizabeth.disbrow@lsuhs.edu
- Julie Knight
  - Julie.Knight@la.gov

Join the Provider Education Network!

- Well-Ahead Louisiana's Provider Education Network provides tools, training and technical assistance that can help you provide the best possible care to our communities
  - Biweekly Newsletters + Real-Time Email Alerts
  - Education and Training Opportunities
  - Community Linkage Coordination
  - Workforce Recruitment and Retention Support
- Learn More: www.wellaheadla.com/move-well-ahead/provider-education-network

Thank You for Joining Us!