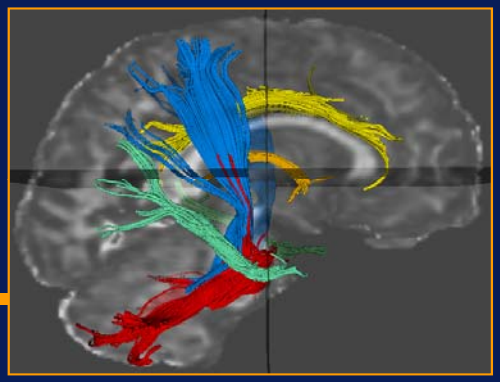
Workshop on Diffusion Tensor Imaging
Clinical Research Applications
University of California, San Francisco
7 June 2011



Diffusion Tensor Imaging: Aging and Alcoholism

Adolf Pfefferbaum and Edith V. Sullivan

SRI International

Stanford University School of Medicine

Supported by NIAAA and NIA

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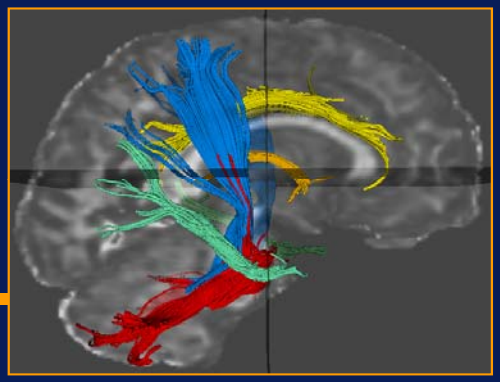


Disclosures

Funding

- NIAAA
- NIA
- SRI International

Conflicts of Interest

- None

Adolf Pfefferbaum and Edith V. Sullivan

SRI International

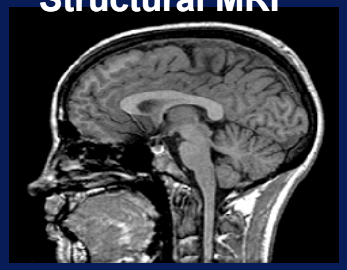
Stanford University School of Medicine

Neuroscience Program

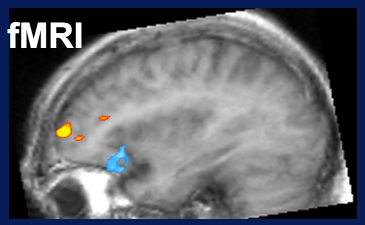
Brain-Behavior Relationships

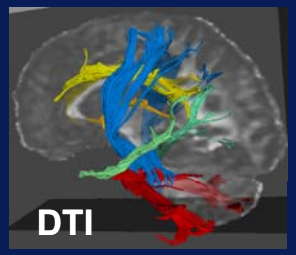
MR Neuroimaging

Structural MRI

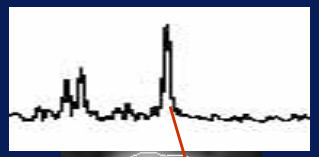


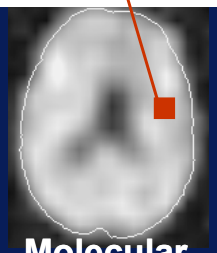
fMRI



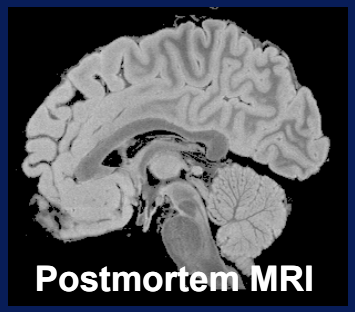


DTI





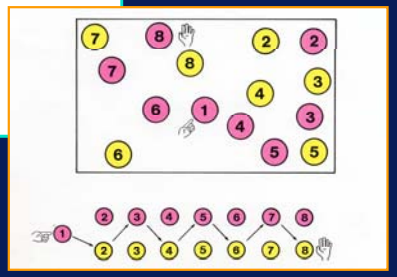
Molecular Spectroscopy



Postmortem MRI

Neuropsychology

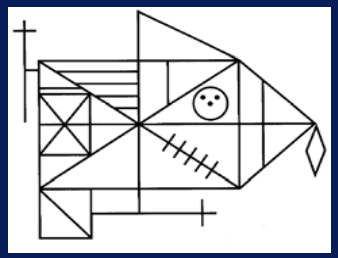
Name the color:
BLUE
GREEN
YELLOW



Executive Functions

Gait & Balance

Components of Memory
- declarative
- procedural
- working
- remote
- verbal
- nonverbal



Visuospatial Functions

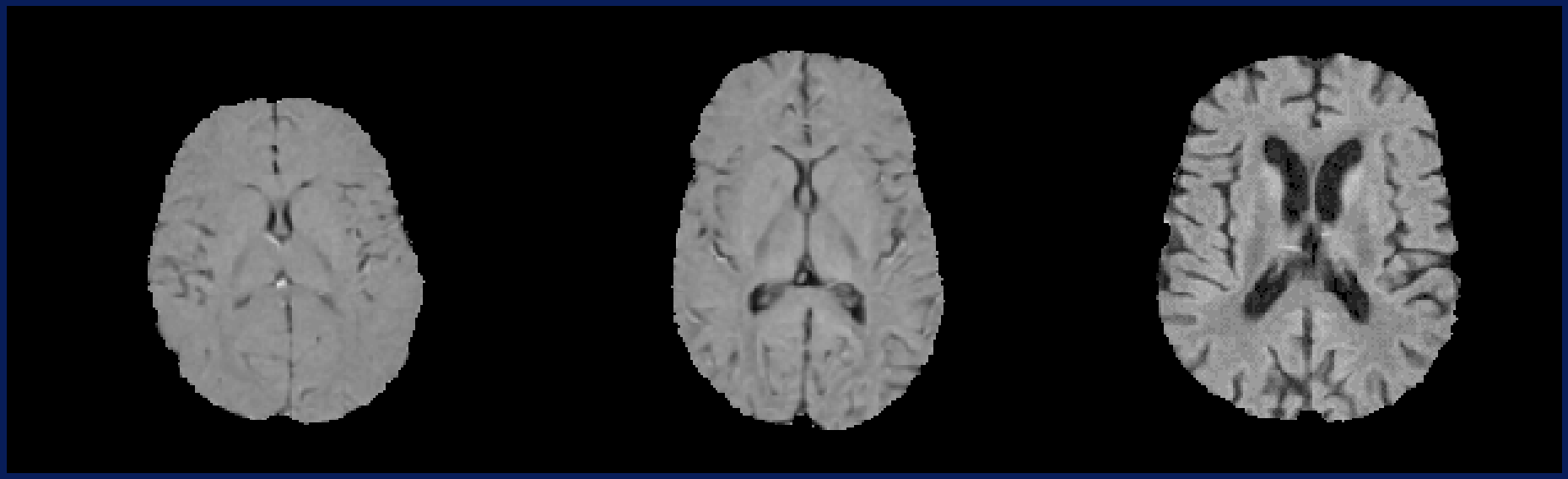
Motor Speed & Learning

White Matter Integrity
Age, Alcoholism, and Function

- Imaging brain white matter in normal aging
  - Macrostructural volumes
  - Microstructural constituents
  - Genetic contribution to structure
- White matter integrity and function in age
- White matter integrity and function in alcoholism
- White matter integrity and connectivity

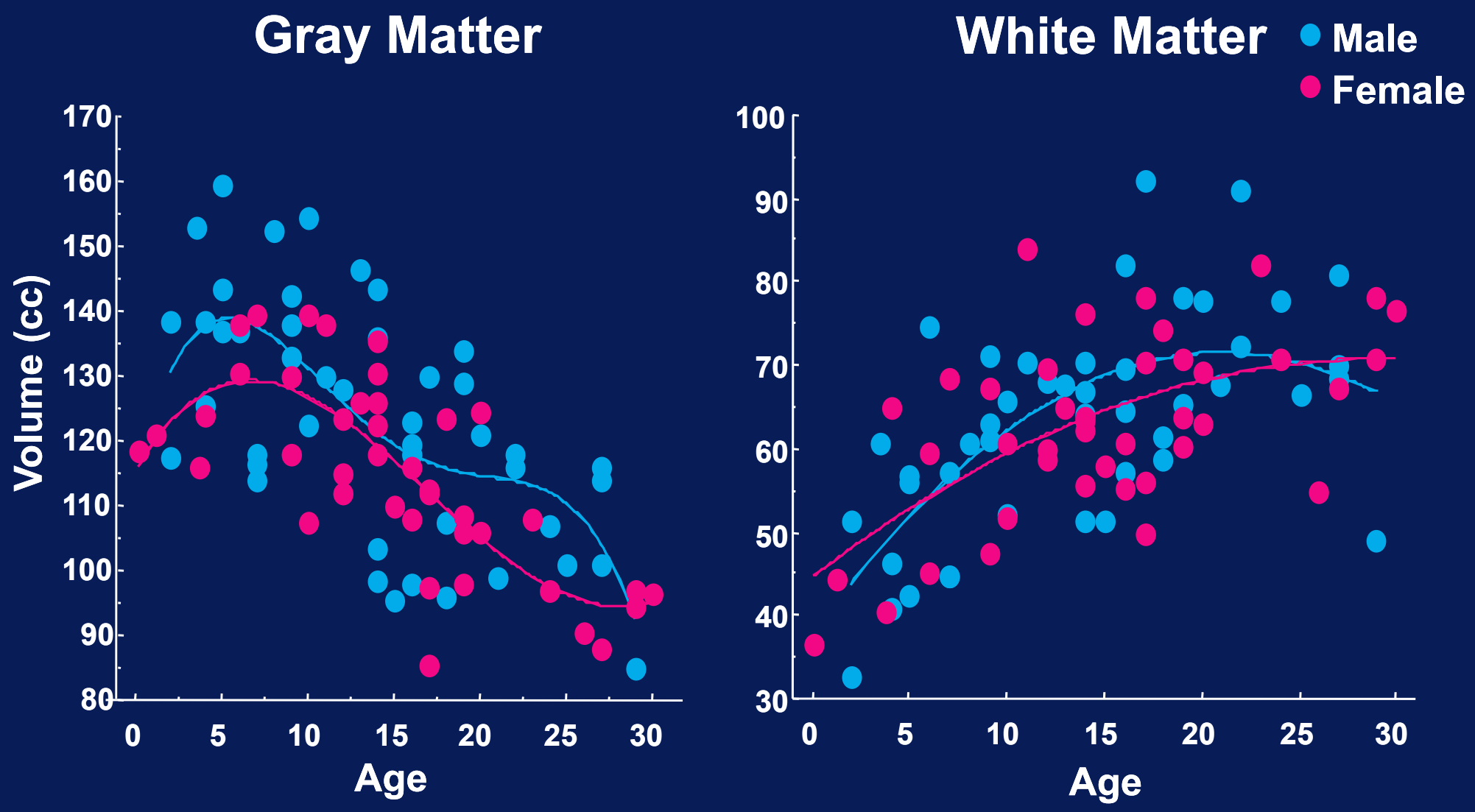
Brain Development and Aging

1 year old | 18 year old | 76 year old



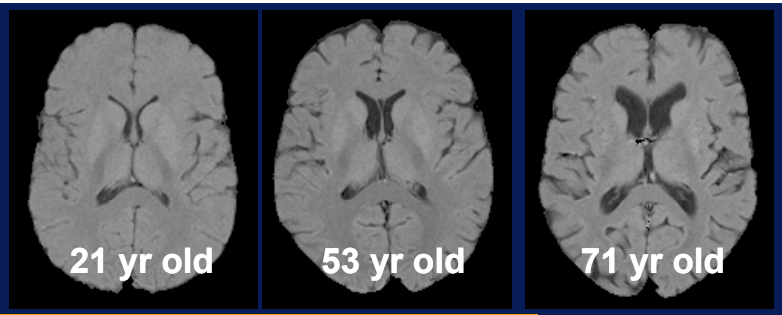
Brain weight increases fourfold from birth to about 10 years of age

Cortical Tissue Volumes

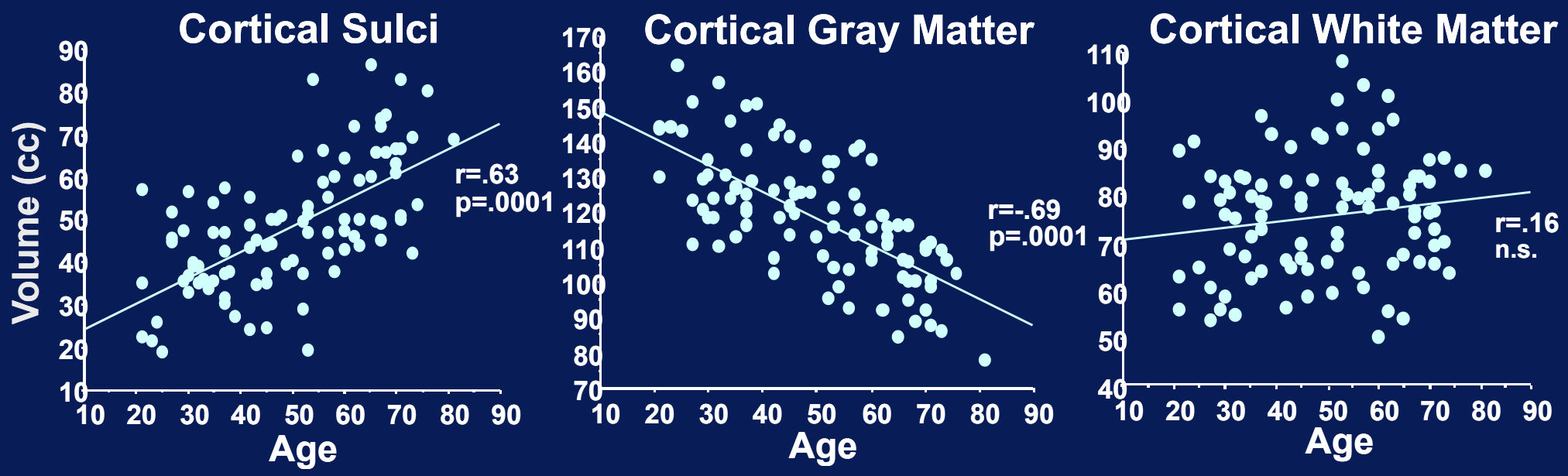


Pfefferbaum et al. *Archives of Neurology* 1994

The Normal Aging Brain

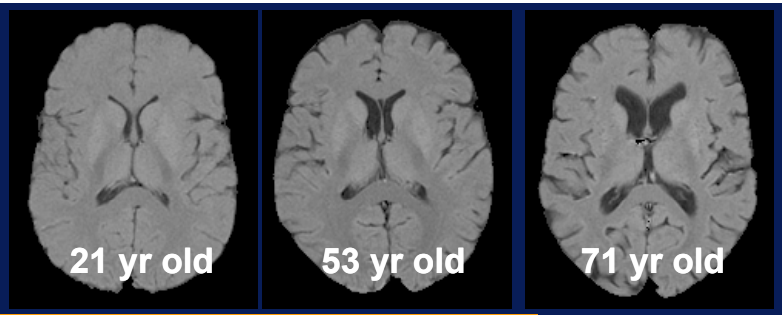


95 Normal Healthy Men

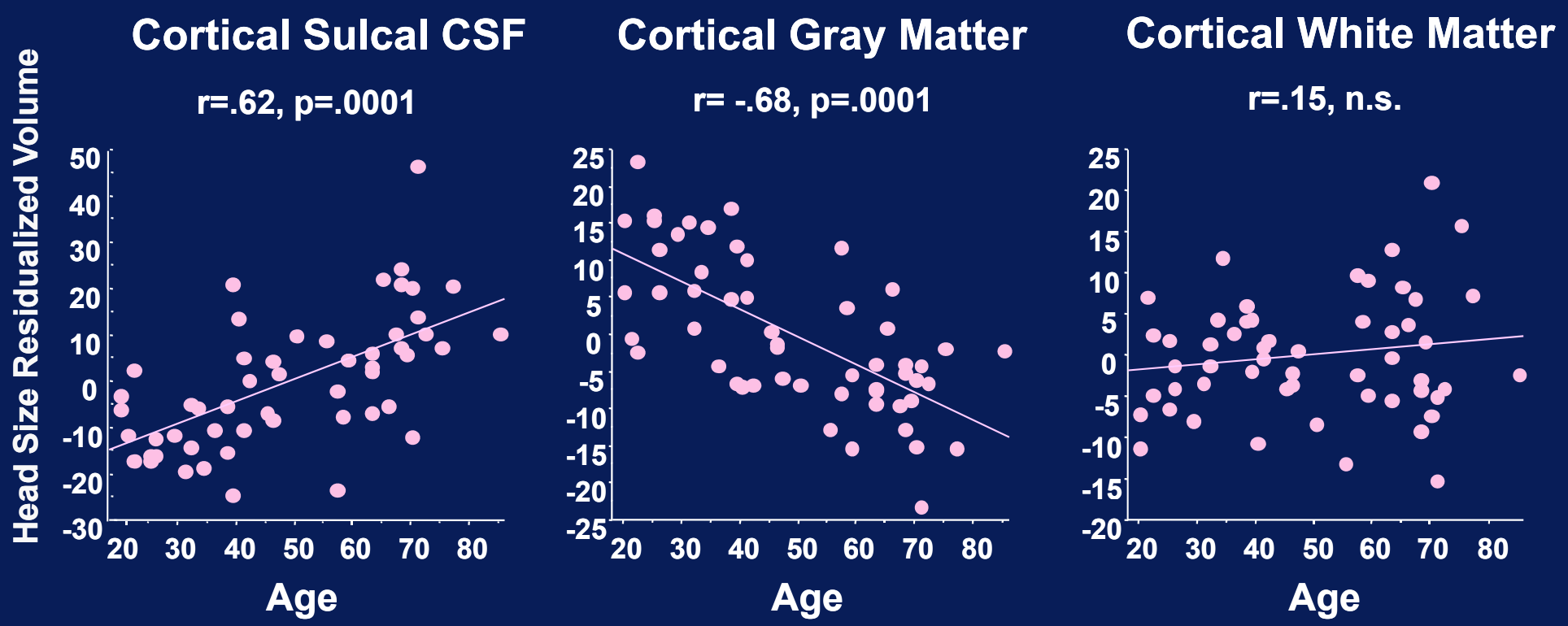


Pfefferbaum et al. *Archives of Neurology* 1994

The Normal Aging Brain



54 Normal Healthy Women

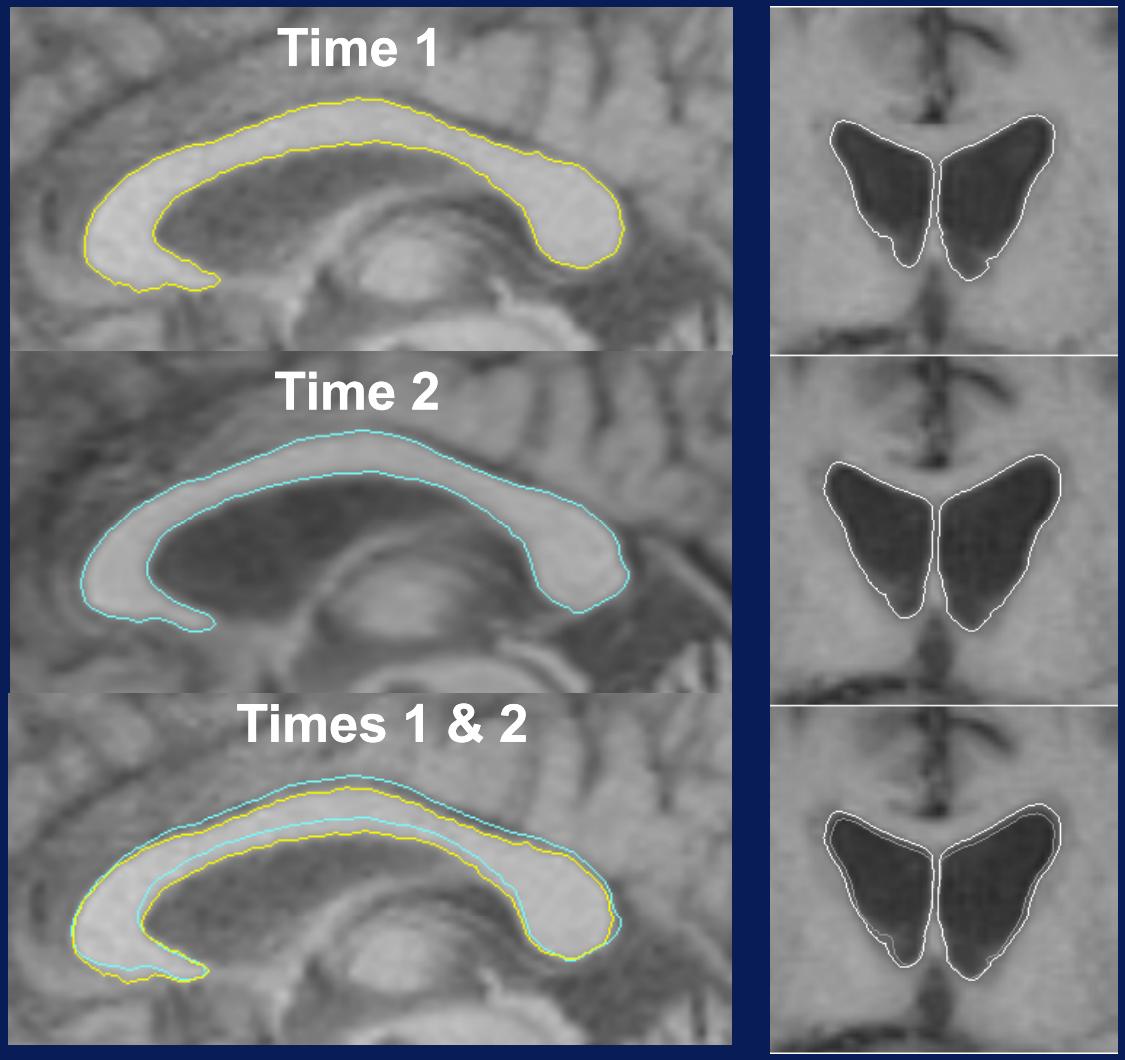


Sullivan et al. *Neurobiology of Aging* 2004

Callosal vs. Ventricular Aging

Differential Rates of Change over 4 Years

215 Men, age 70-82 years old



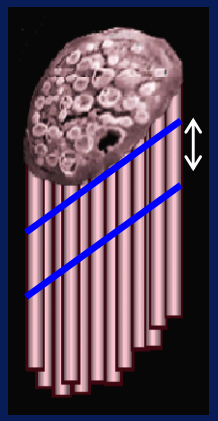
- Annual ventricular expansion=2.9%
- Annual callosal shrinkage=-0.9%

- Change in size and morphology of the corpus callosum largely due to ventricular expansion

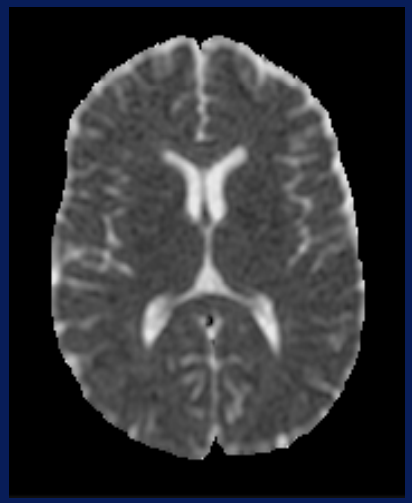
Sullivan et al. *Cerebral Cortex* 2005

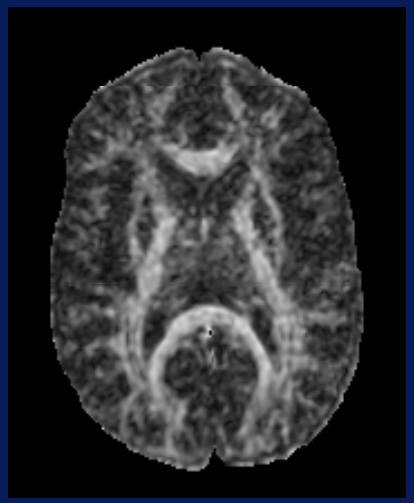
MR Diffusion Tensor Imaging (DTI)

- Index of microstructural integrity (e.g., in white matter, myelin)
  - » Intravoxel coherence: measures magnitude (diffusivity) and orientation (anisotropy) of freely diffusing water molecules within individual voxels



Diffusivity Image (CSF brightest)

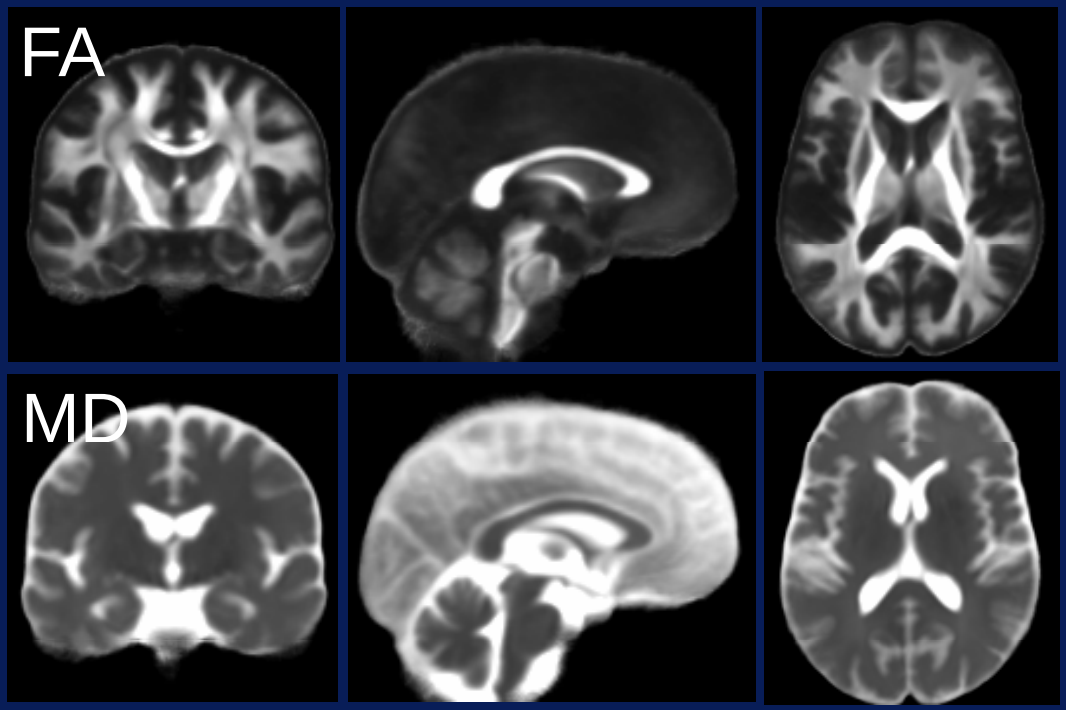




Fractional Anisotropy Image (White matter brightest)

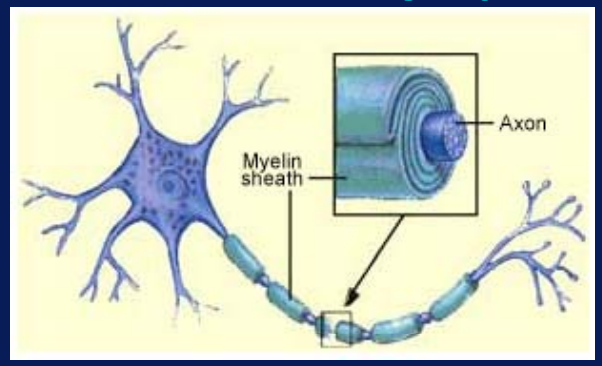
- ➢Small macrostructural change in white matter volume with age
- ➢Is there detectable microstructural change?

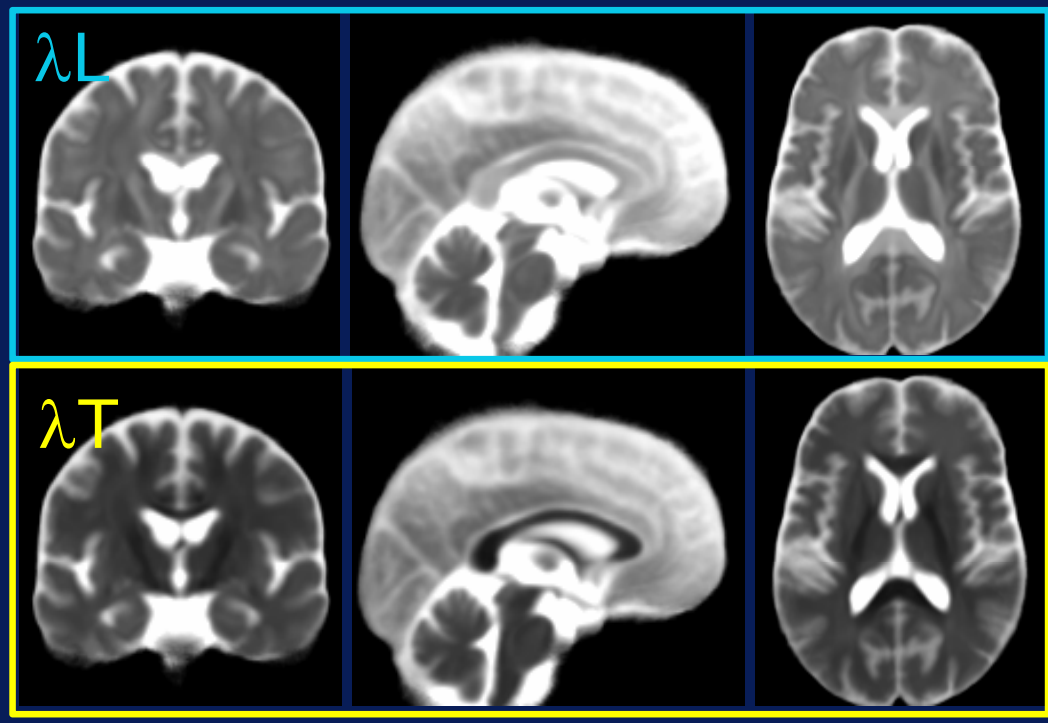
DTI Metrics

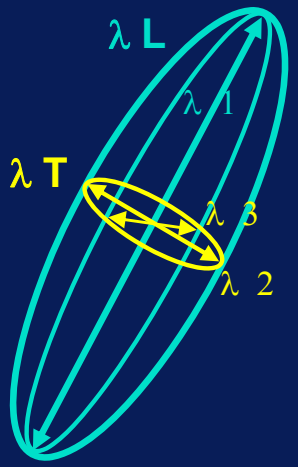


Axonal integrity

λL







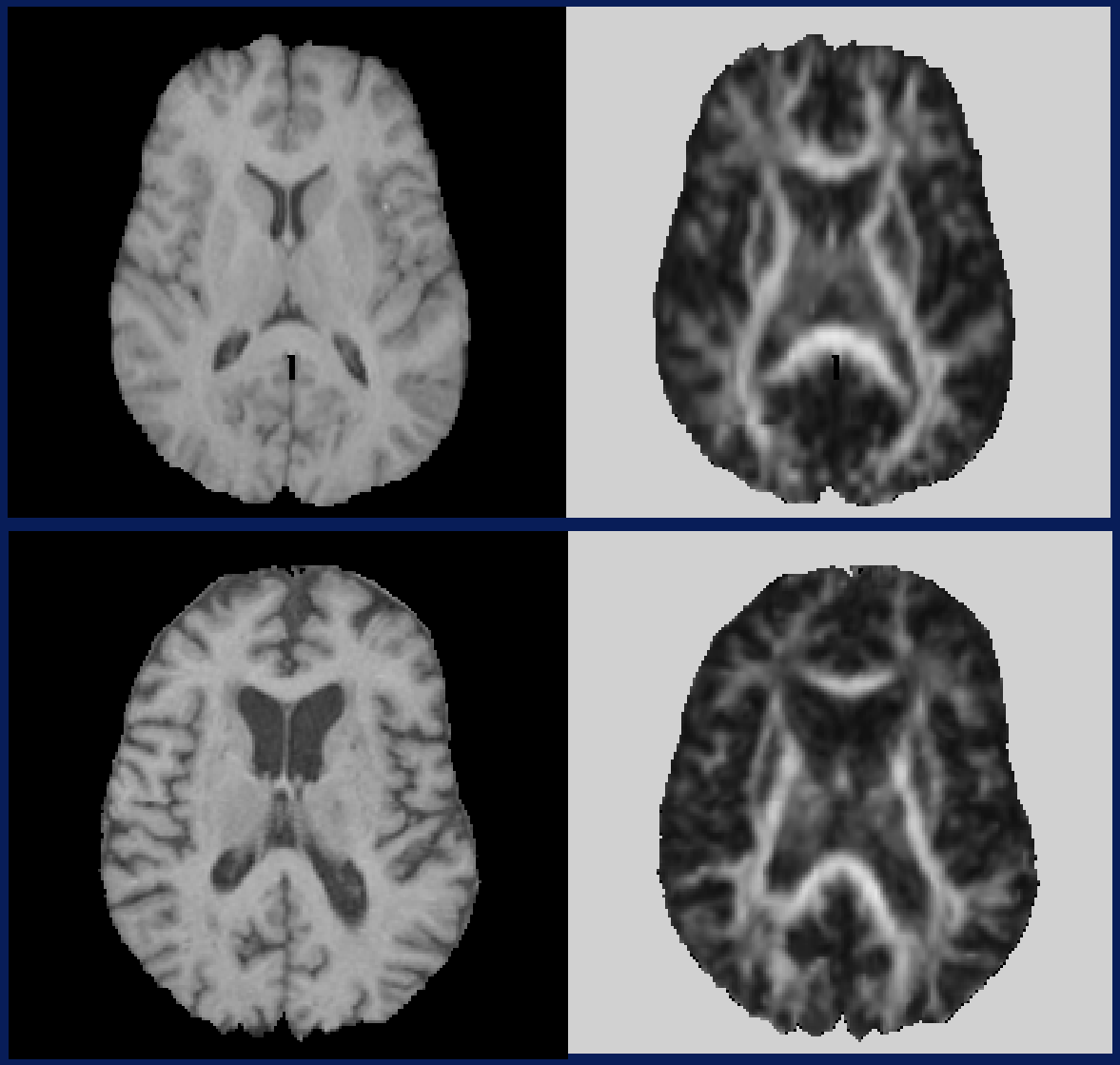
Myelin integrity

λT

Normal Aging of White Matter Microstructure: Partner MRI+DTI

31 yr old

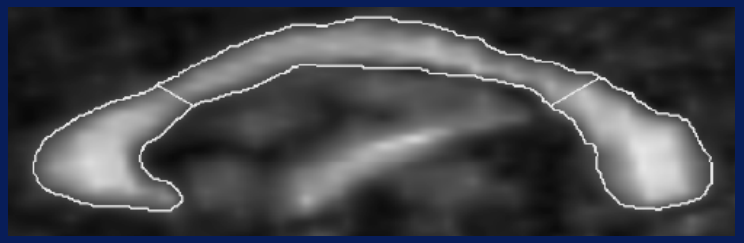
71 yr old



Pfefferbaum & Sullivan. In *Clinical MR Neuroimaging: Diffusion, Perfusion & Spectroscopy (2nd ed)* 2010

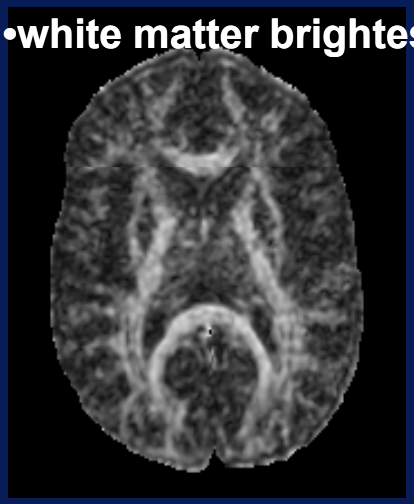
Normal Aging

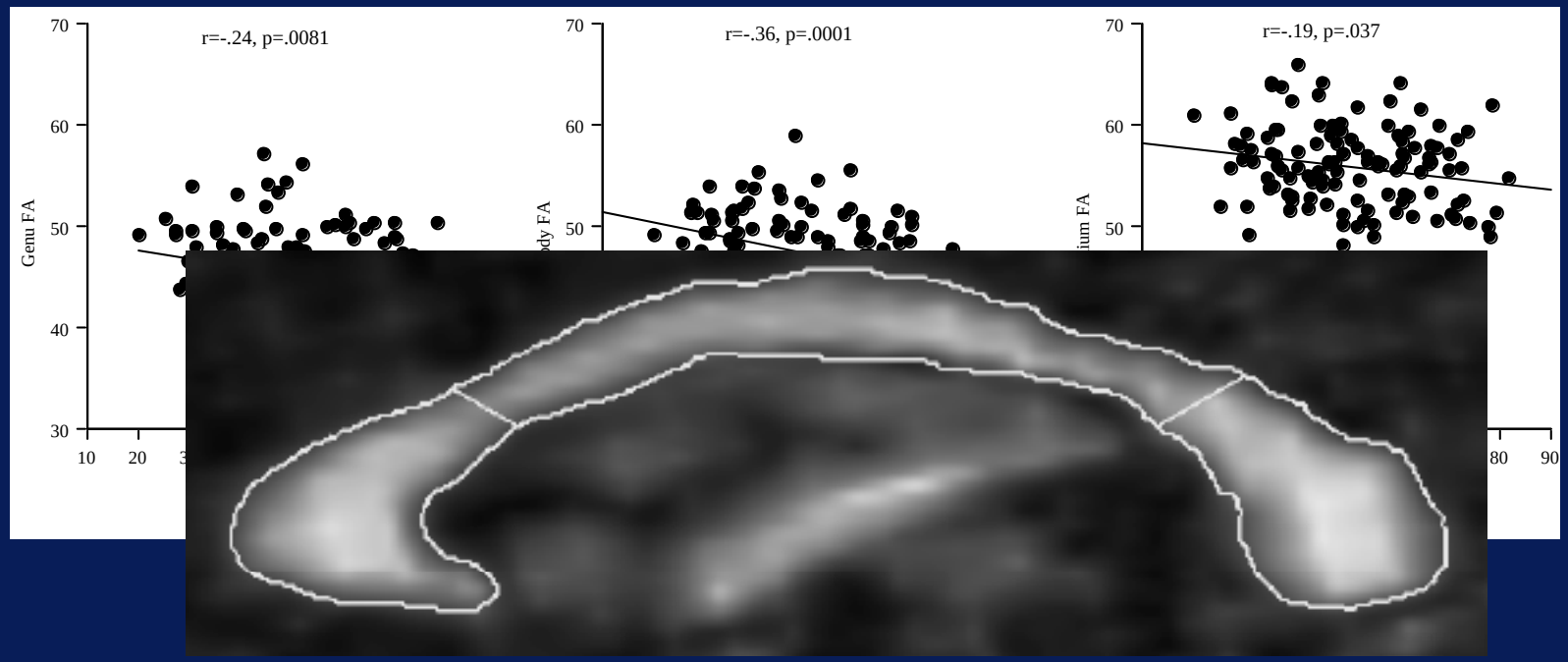
Corpus Callosum Microstructure



FA Image

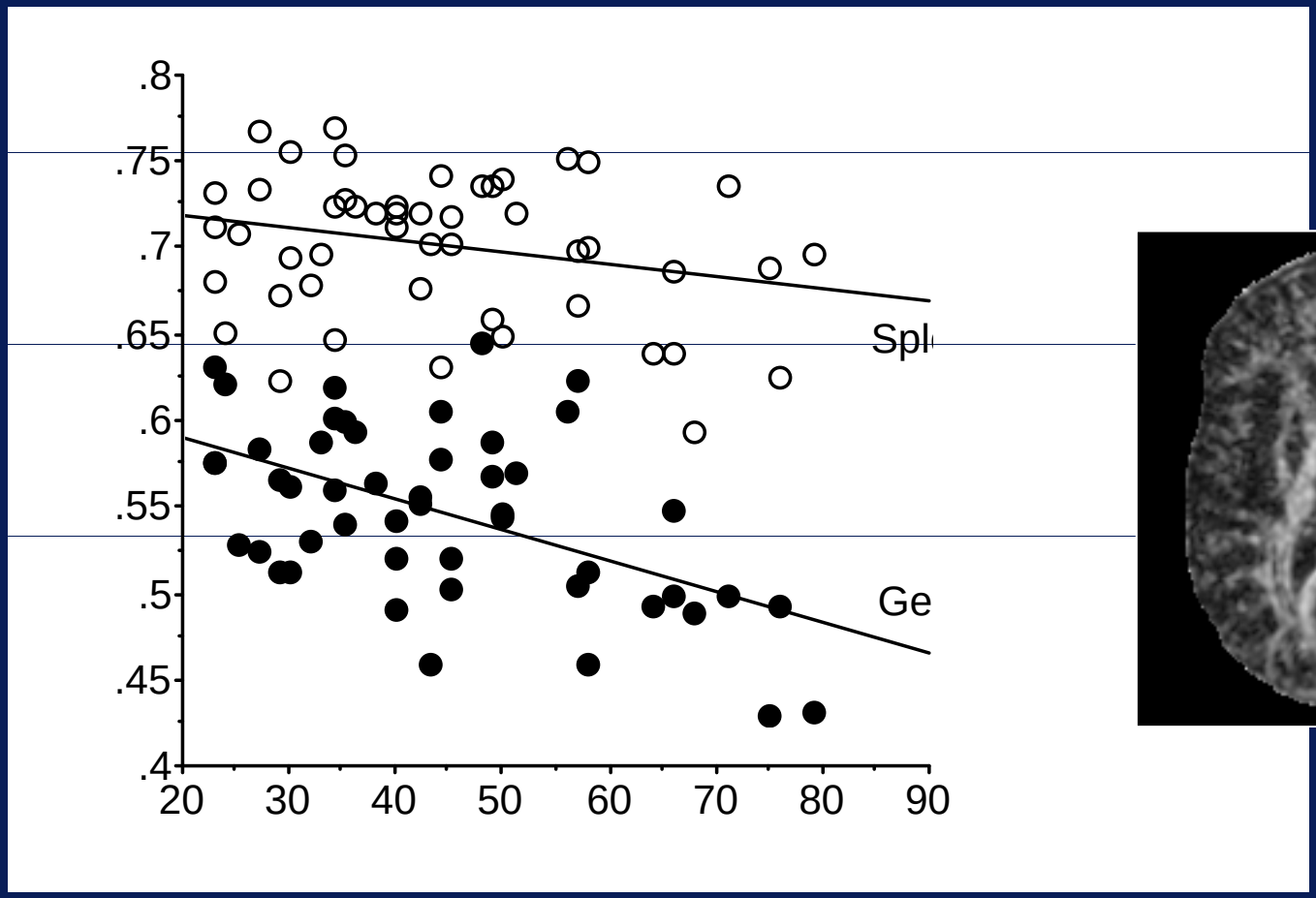
- orientation of diffusion
- white matter brightest

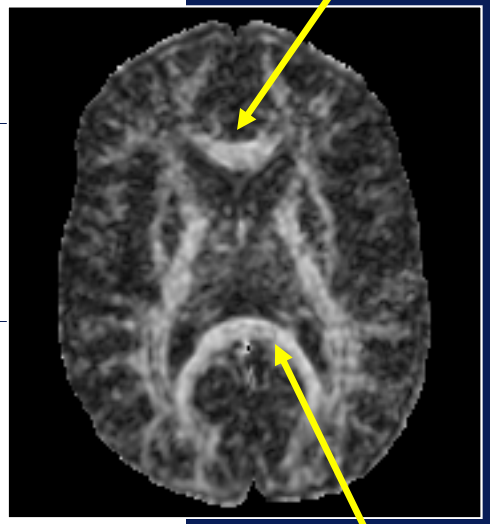




Pfefferbaum et al. *Brain* 2007

Age Effect in the Anterior Corpus Callosum



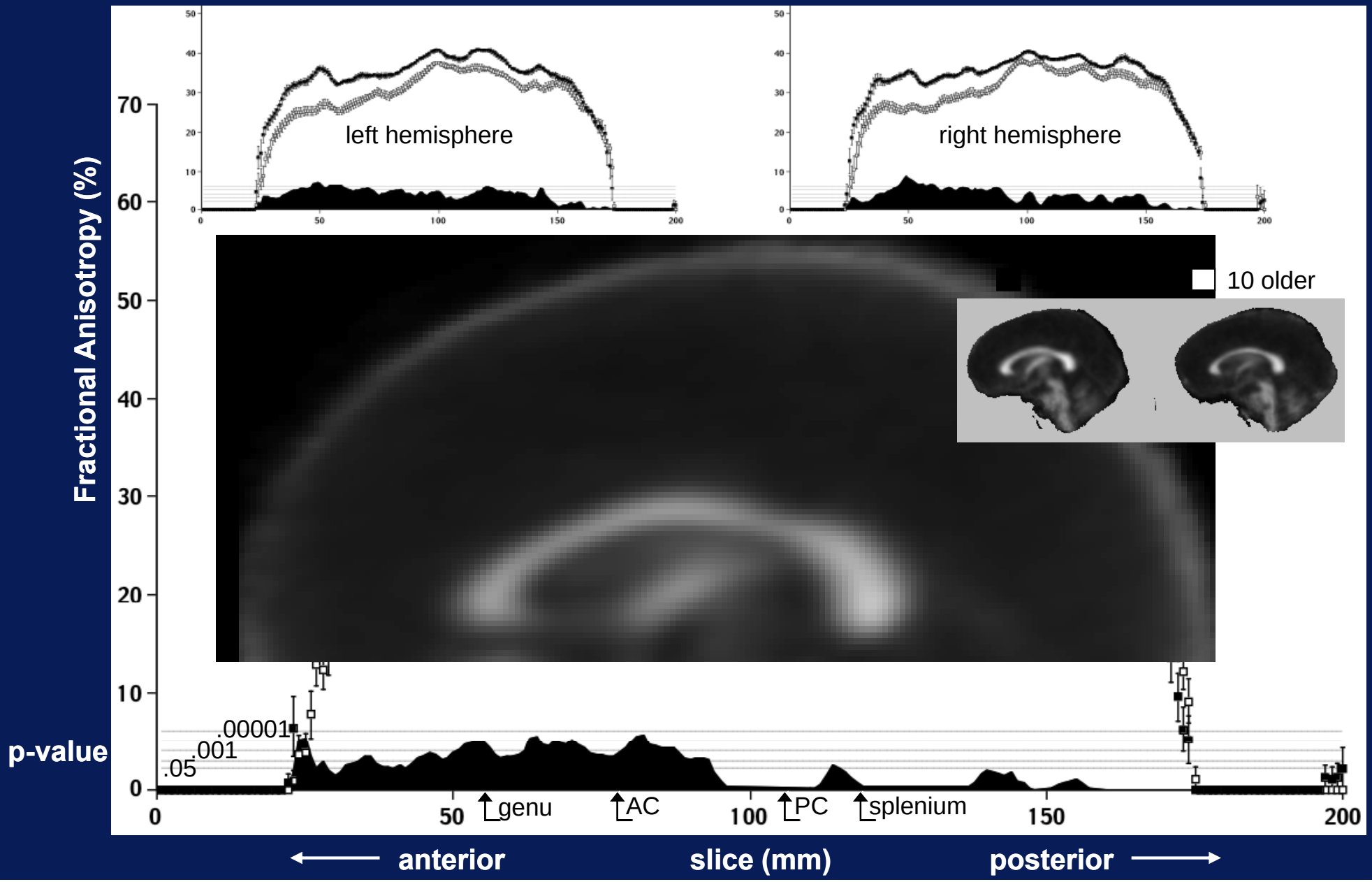


Sullivan et al. *NeuroReport* 2000

Pfefferbaum, Adalsteinsson, Sullivan
NeuroImage 2005

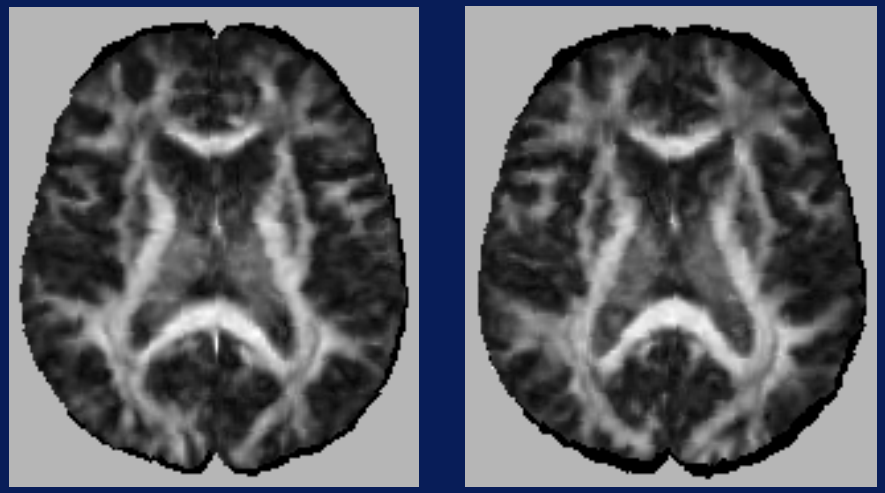
Frontal Distribution

Age Effects on Supratentorial White Matter FA

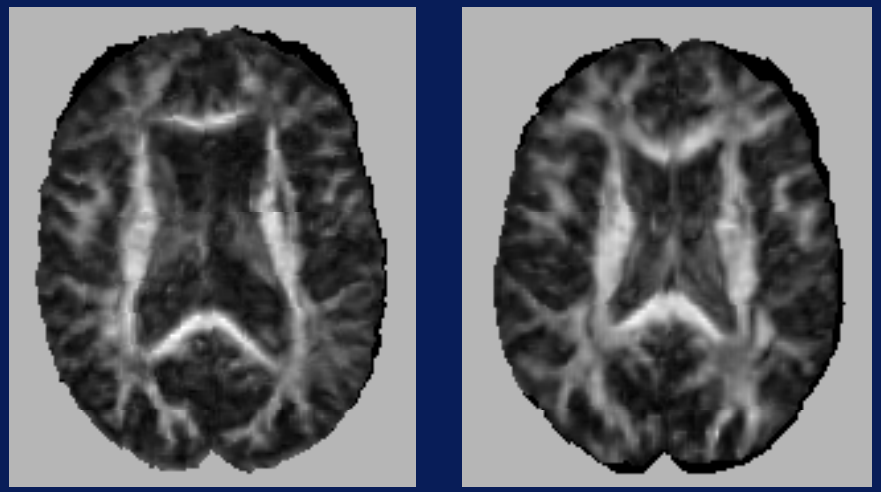


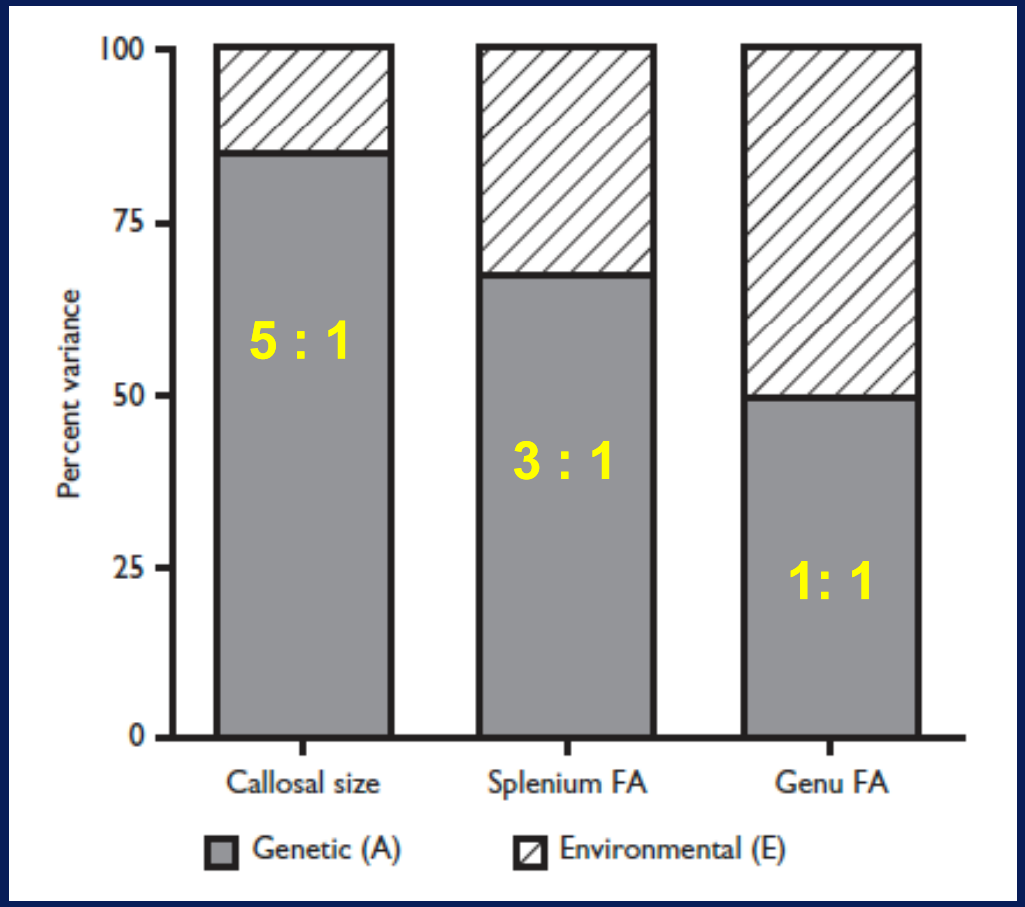
Heritability of Callosal FA

14 MZ Twin Pairs



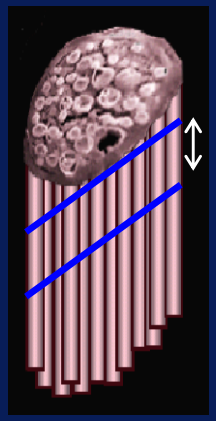
18 DZ Twin Pairs





Pfefferbaum, Sullivan, Carmelli *NeuroReport* 2001

Quantitative Fiber Tracking



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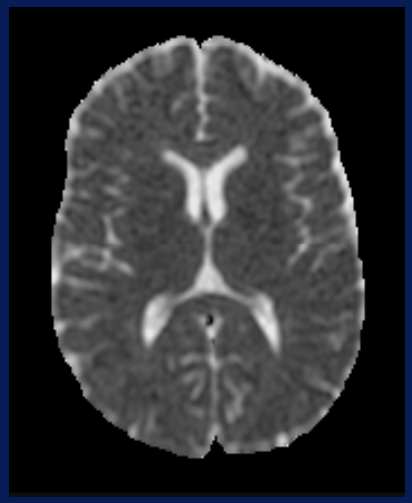
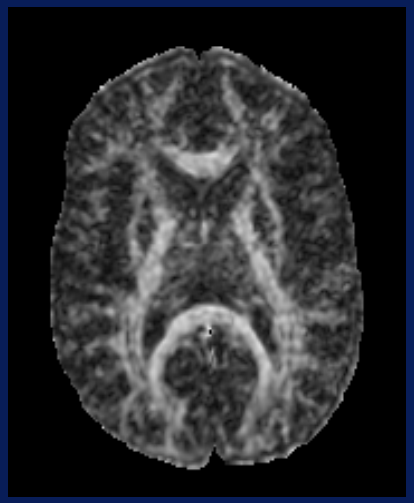
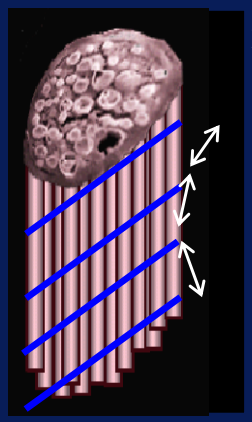
Diffusivity Image (CSF brightest)



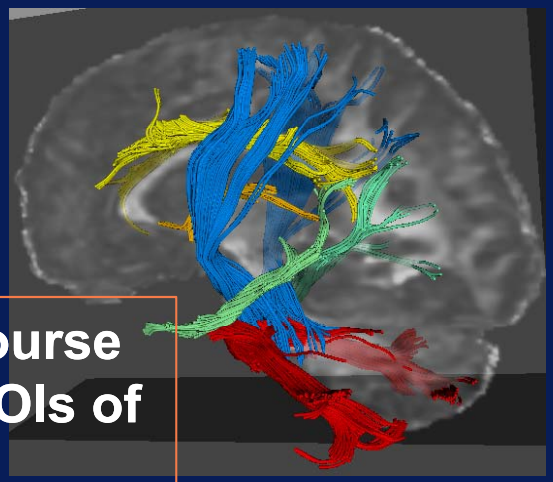


Fractional Anisotropy Image (White matter brightest)

FA in anatomically defined ROIs of corpus callosum

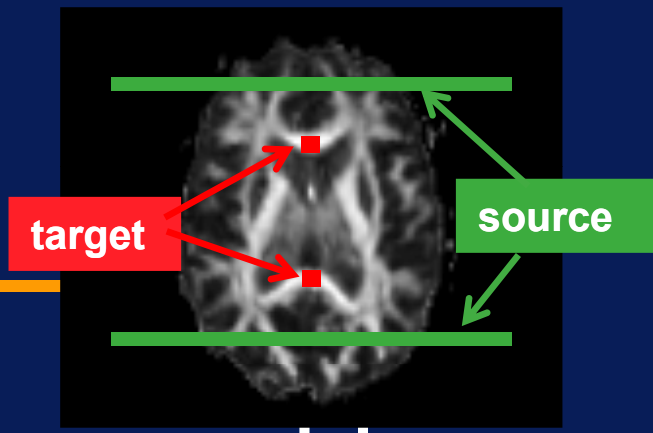


» Intervoxel coherence: measures anisotropy and diffusivity on a voxel-to-voxel basis for (quantitative) fiber tracking

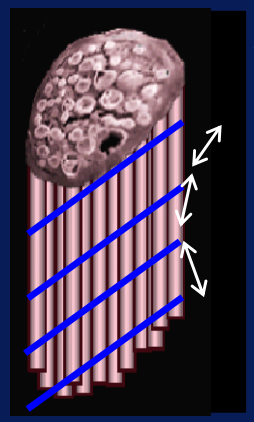


FA in fibers that course through defined ROIs of corpus callosum

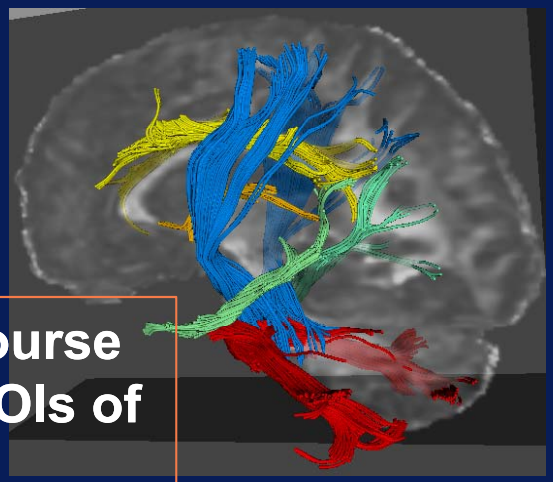
Quantitative Fiber Tracking



- Identify fibers with a target and source model
- Compute FA and diffusivity along the entire fiber bundle, number of fibers, fiber length
- Examine central, proximal, and distal fiber bundle segments



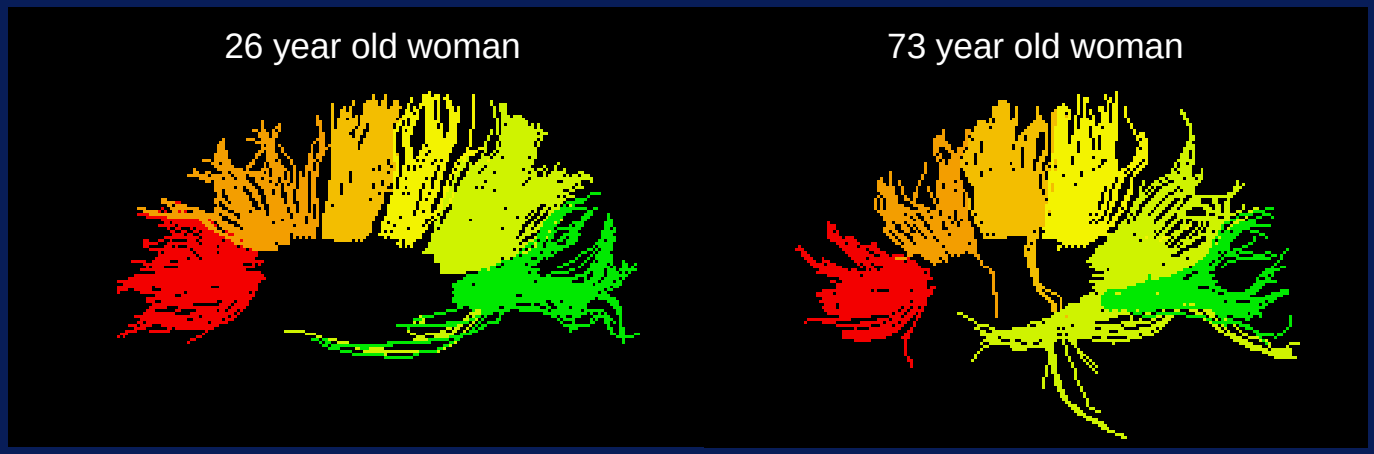
» Intervoxel coherence: measures anisotropy and diffusivity on a voxel-to-voxel basis for (quantitative) fiber tracking

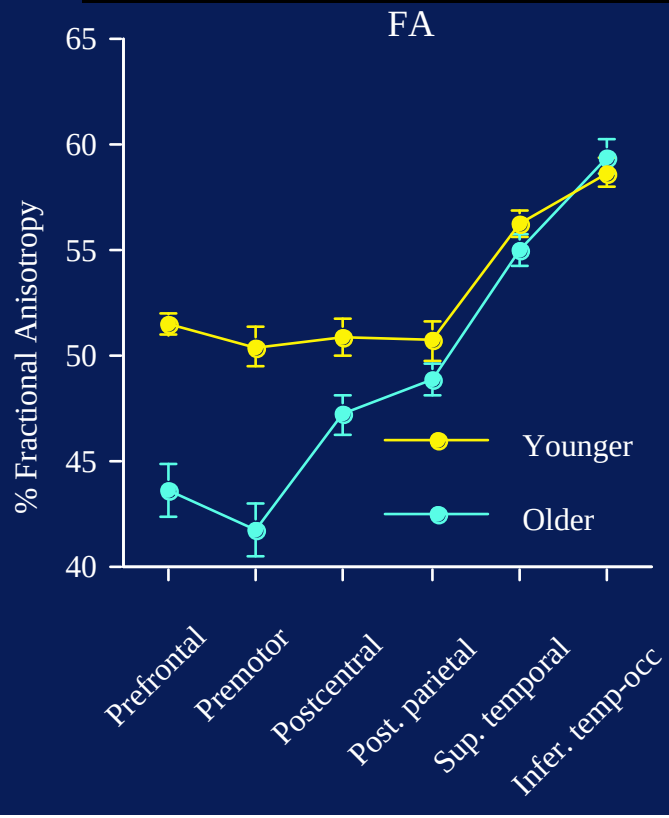


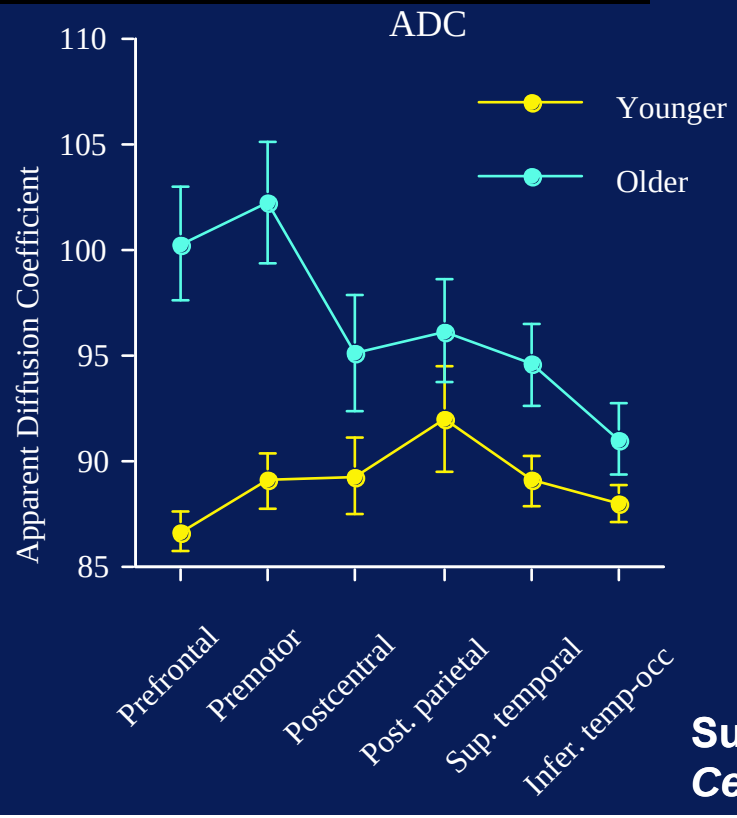
FA in fibers that course through defined ROIs of corpus callosum

Quantitative Fiber Tracking

Fibers Coursing through Corpus Callosum and Age



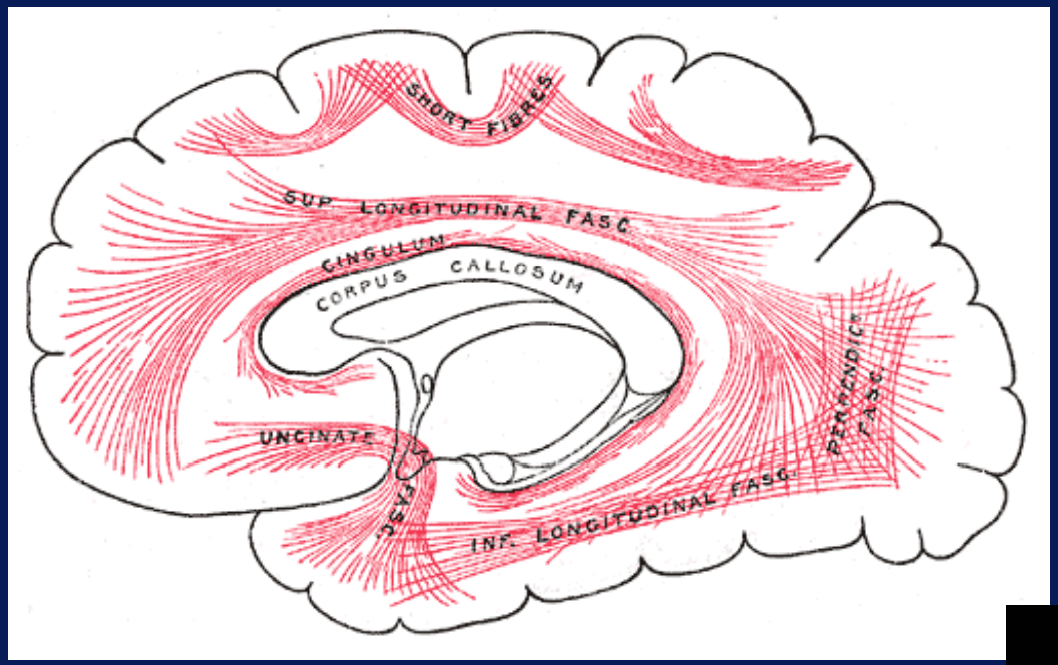


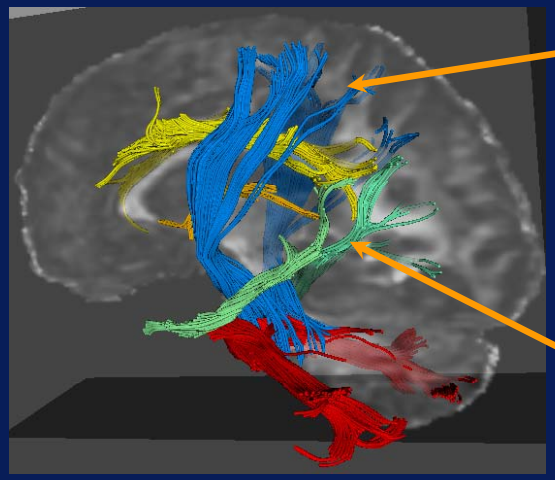


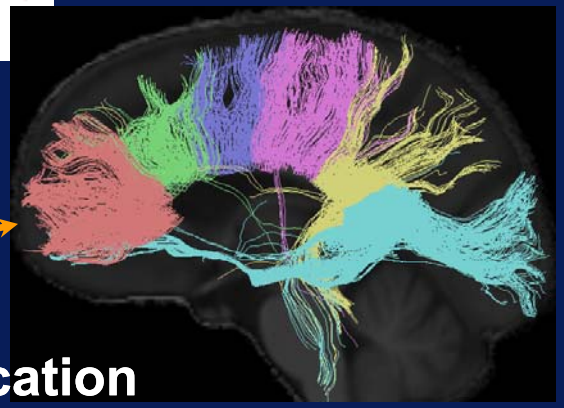
Sullivan et al.
***Cerebral Cortex* 2006**

White Matter Systems and Performance

Pathways of Neural Communication



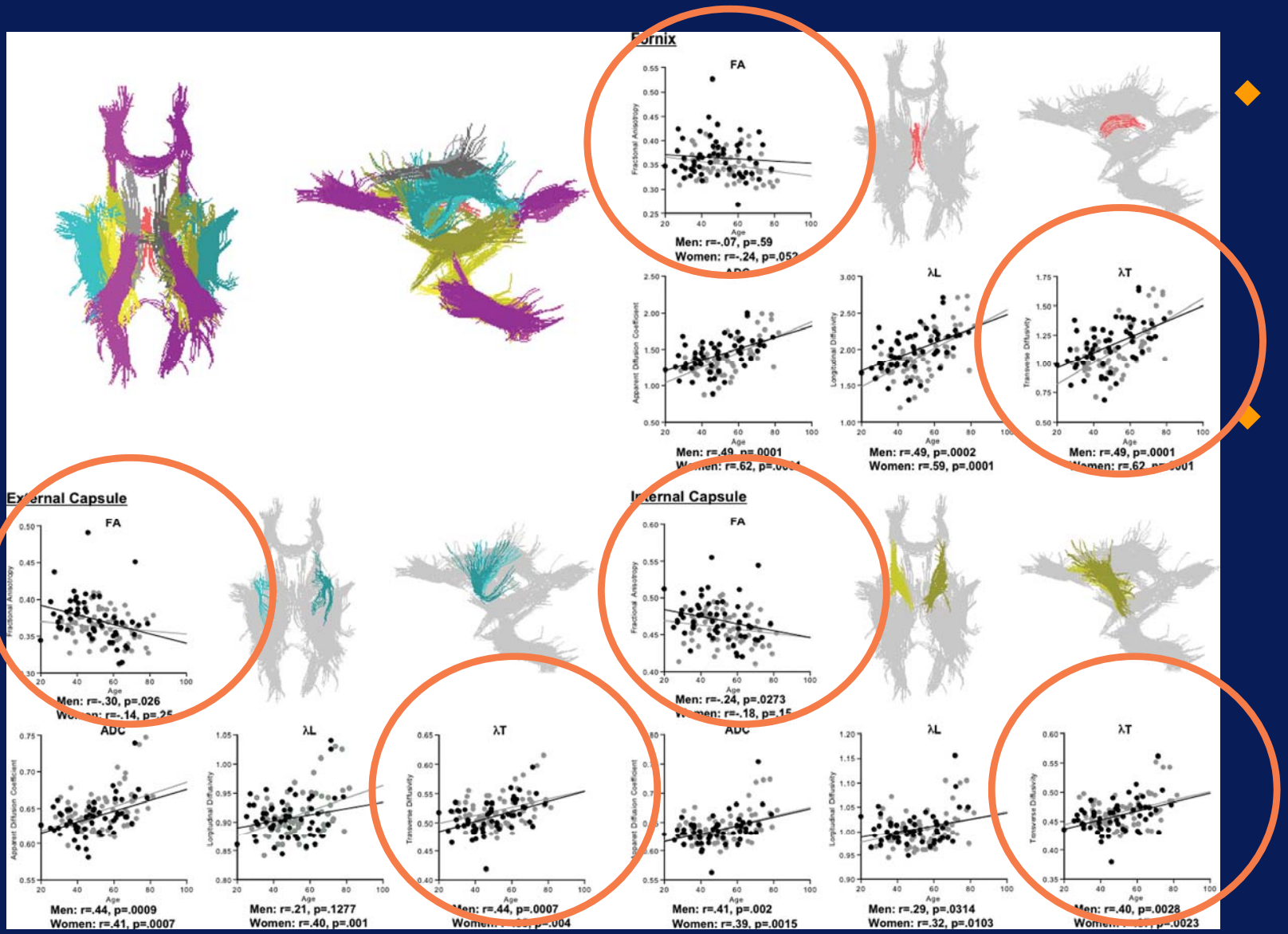




- **Projection fibers**
  - corticospinal tracts
  - pontocerebellar tracts
- **Commissures**
  - interhemispheric communication
- **Association fibers**
  - long fasciculi and short U-fibers
  - intrahemispheric communication

Quantitative Fiber Tracking

Age and Sex (N=120)



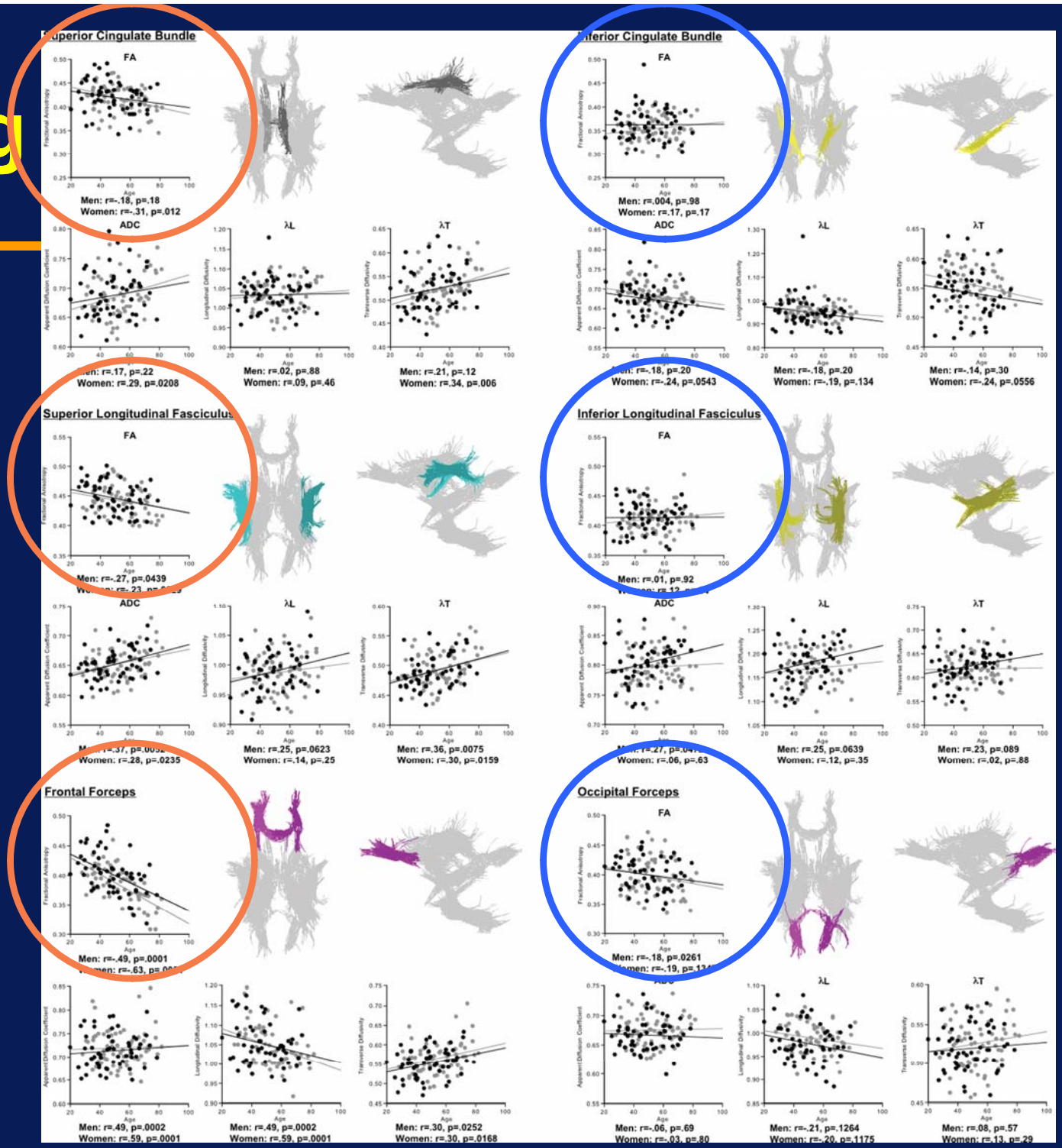
- Diffusivity is more sensitive than FA to age differences in several regions.
- Sex differences over age were seldom observed.

Sullivan, Rohlfing, Pfefferbaum *Neurobiology of Aging* 2010

Fiber Tracking

Age and Sex

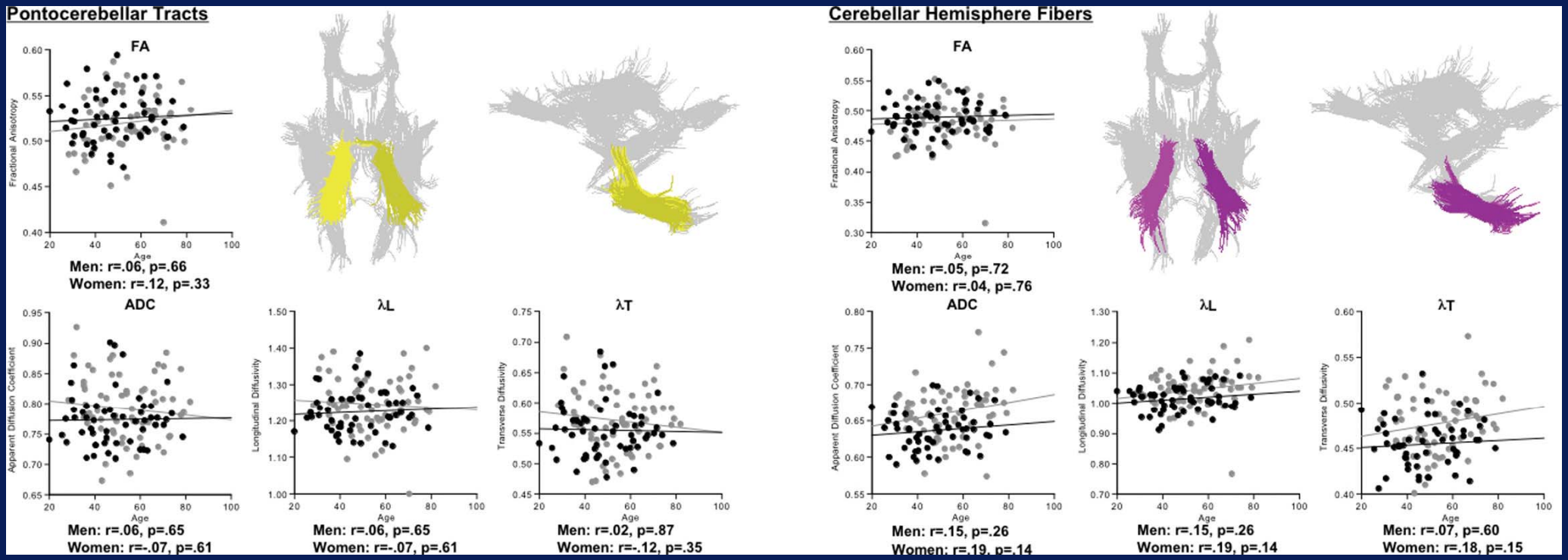
- Superior and Frontal fiber bundles were more vulnerable to age effects than inferior or posterior bundles.
- In general, men and women showed similar regional age effects.



Sullivan, Rohlfing, Pfefferbaum *Neurobiology of Aging* 2010

Quantitative Fiber Tracking

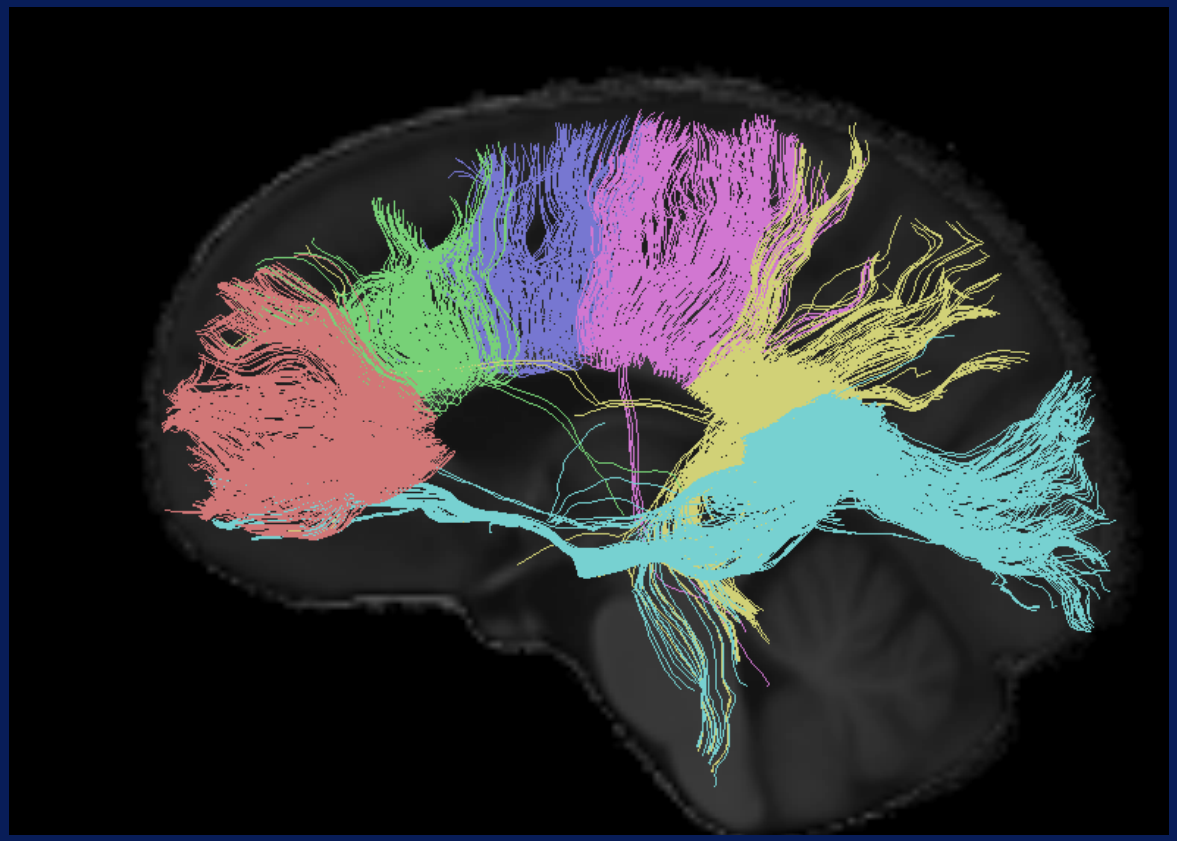
Pontocerebellar Tracts: Age and Sex



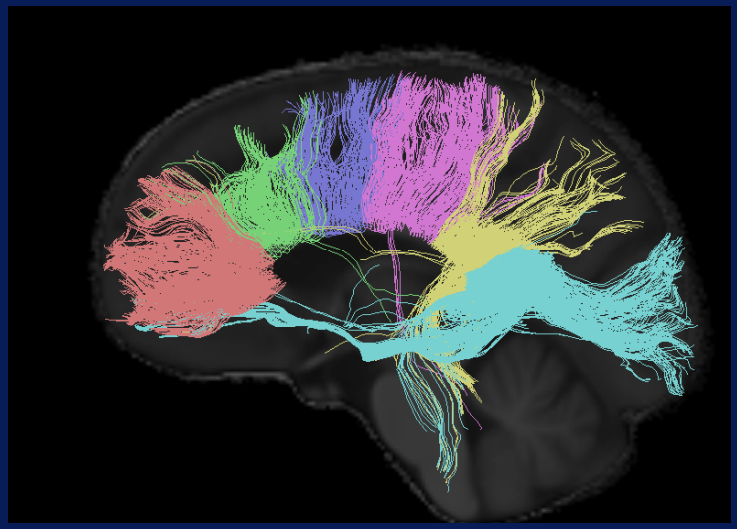
- **Neither age nor sex differences occurred in FA or diffusivity in pontine or cerebellar tracts.**

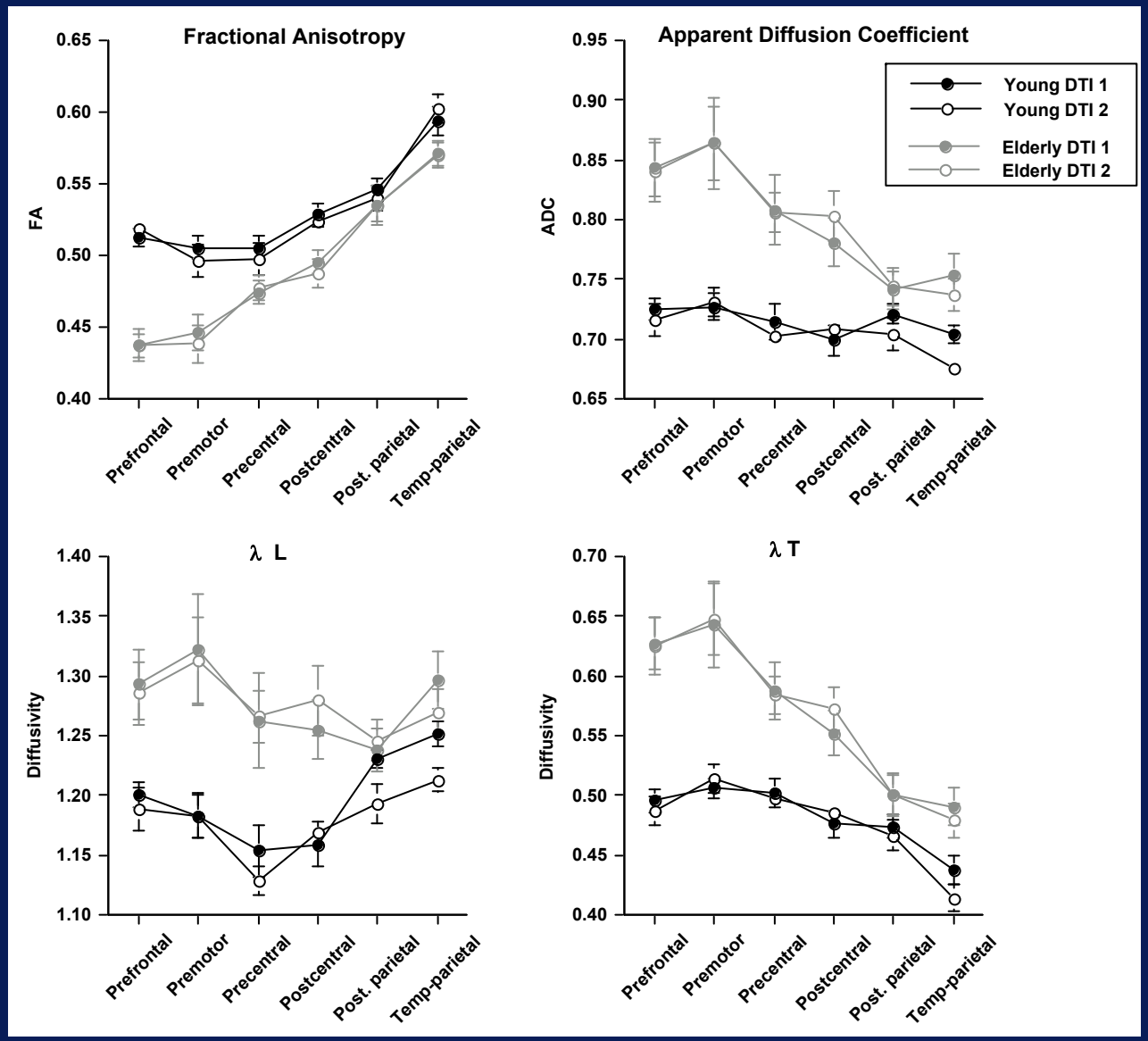
Sullivan, Rohlfing, Pfefferbaum *Neurobiology of Aging* 2010

Progression?



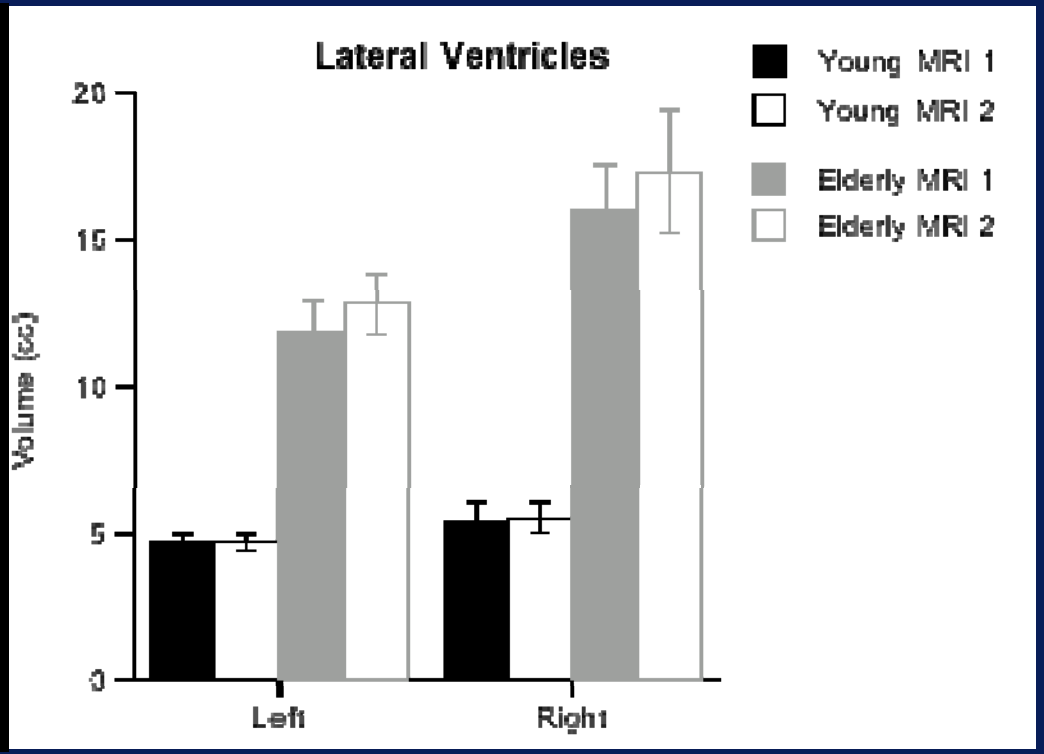
Progression over 2 Years?





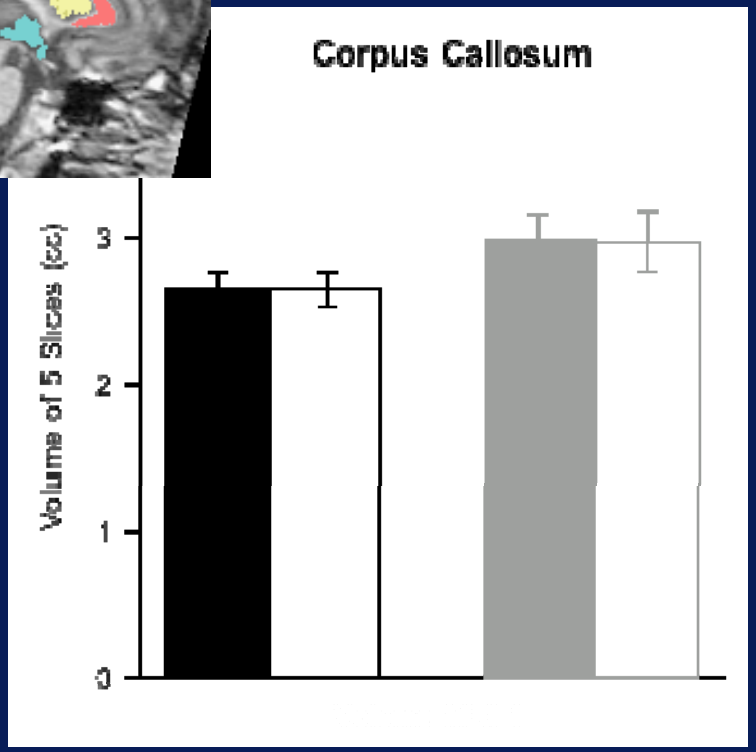
Sullivan, Rohlfing, Pfefferbaum *Developmental Neuropsychology* 2010

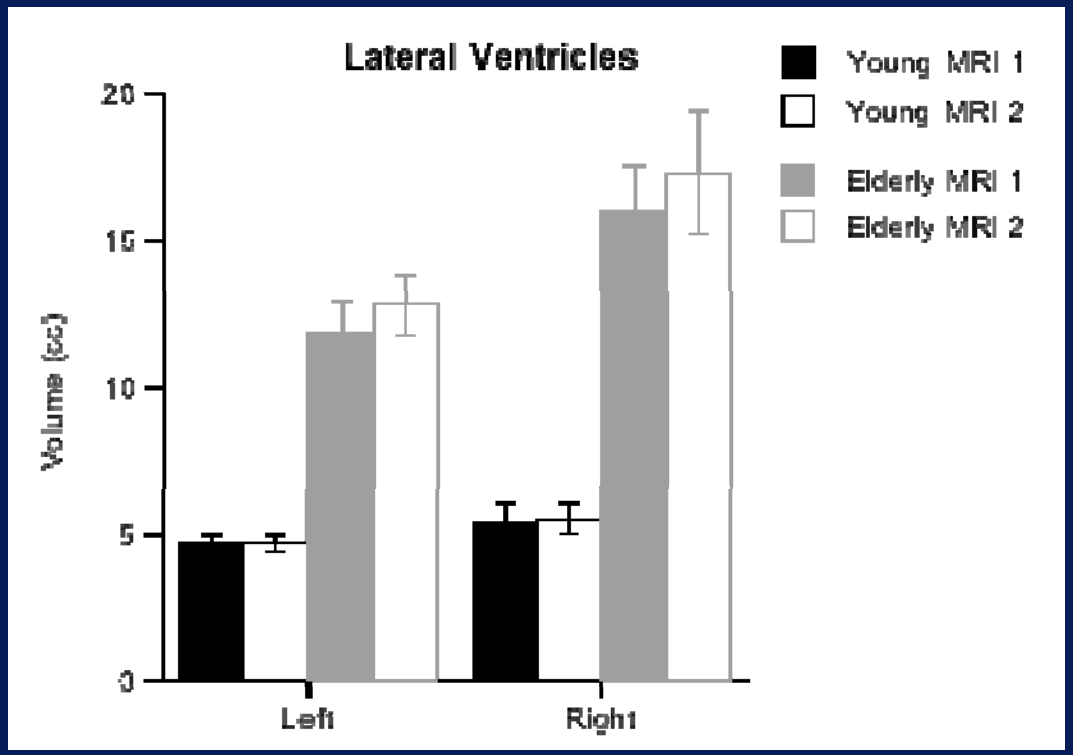
Progression over 2 Years?



Sullivan, Rohlfing, Pfefferbaum *Developmental Neuropsychology* 2010

Progression over 2 Years?

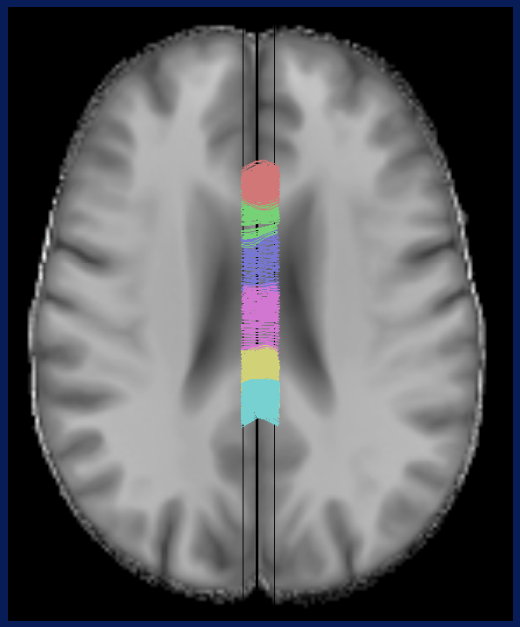


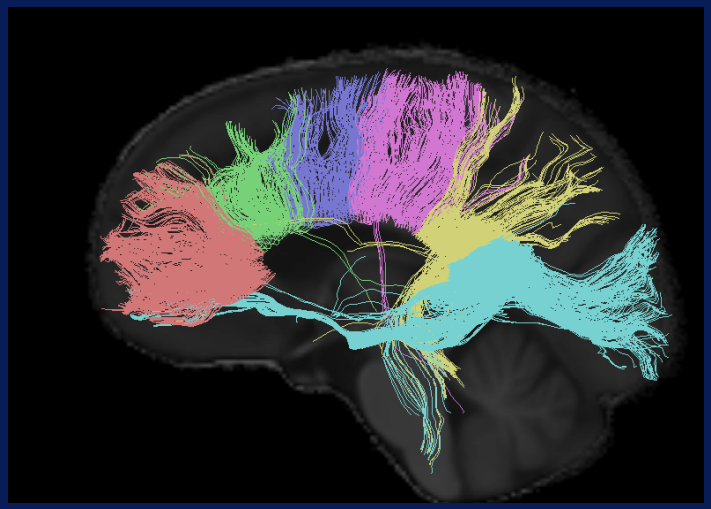


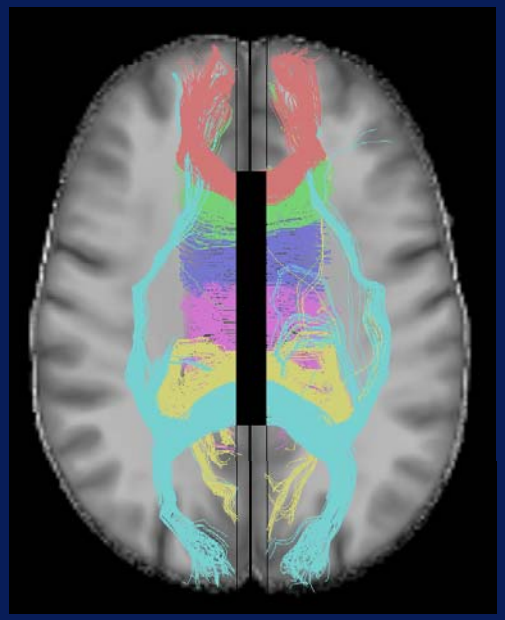
Sullivan, Rohlfing, Pfefferbaum *Developmental Neuropsychology* 2010

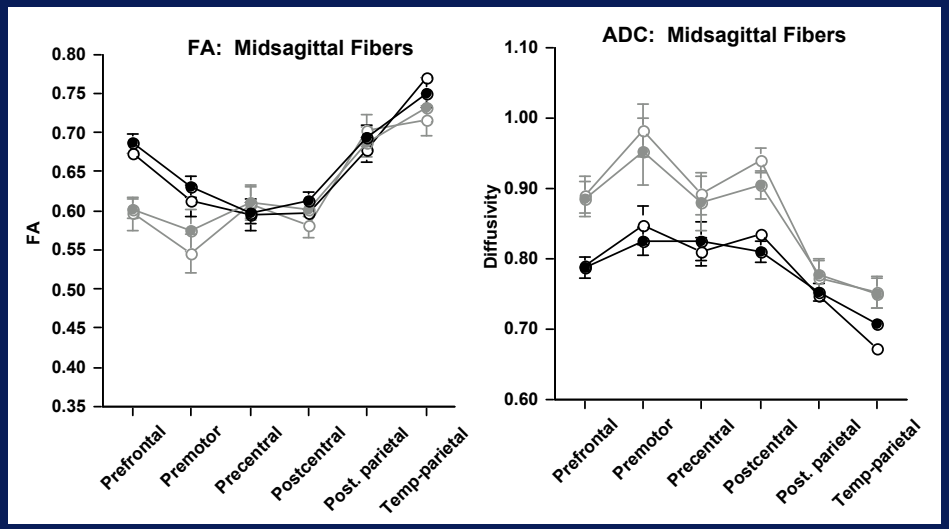
Corpus Callosum and Age

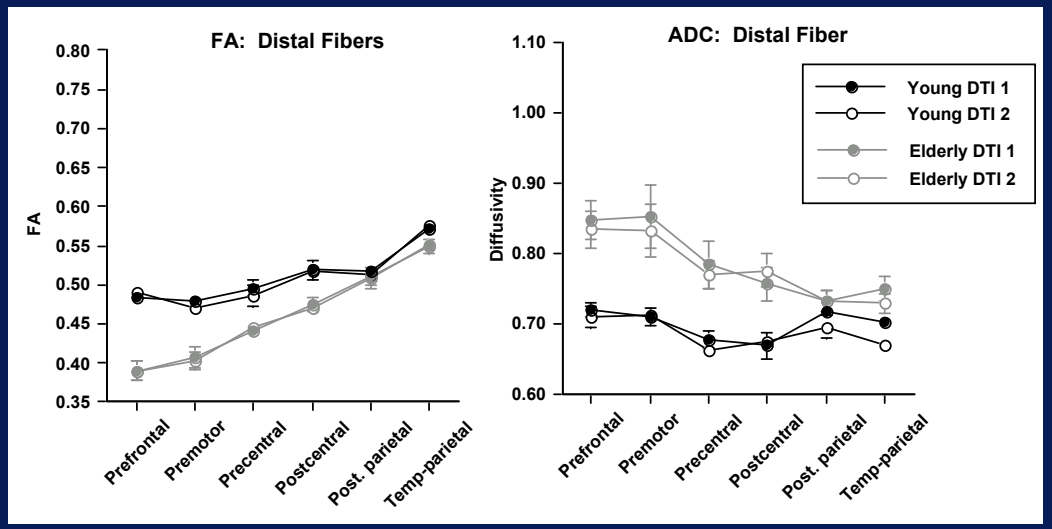
Central vs. Lateral Fibers











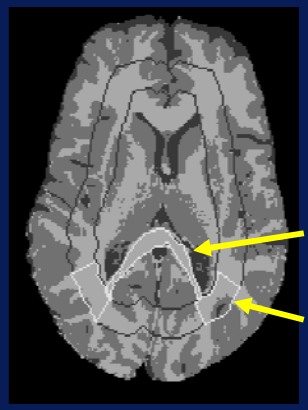
Sullivan, Rohlfing, Pfefferbaum *Developmental Neuropsychology* 2010

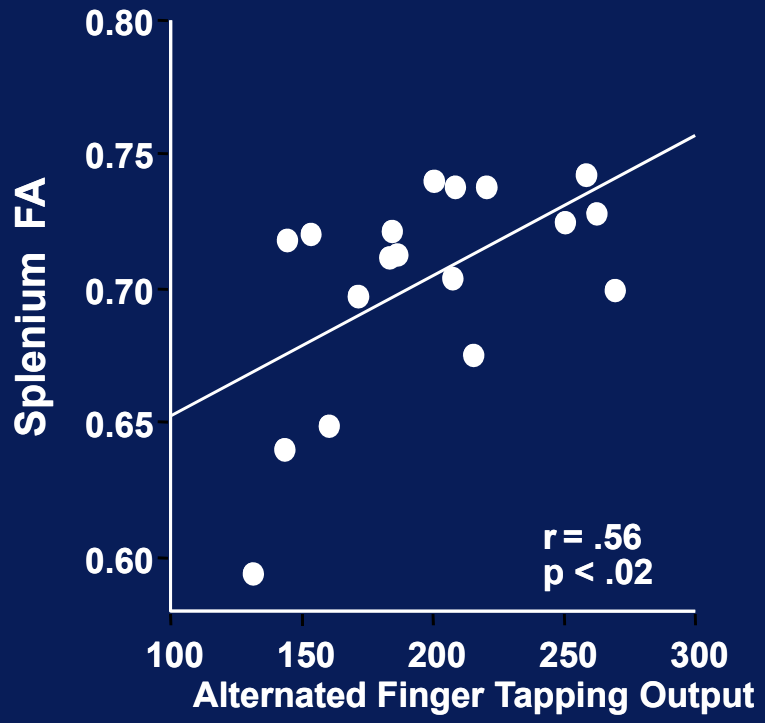
White Matter Integrity
Age, Alcoholism, and Function

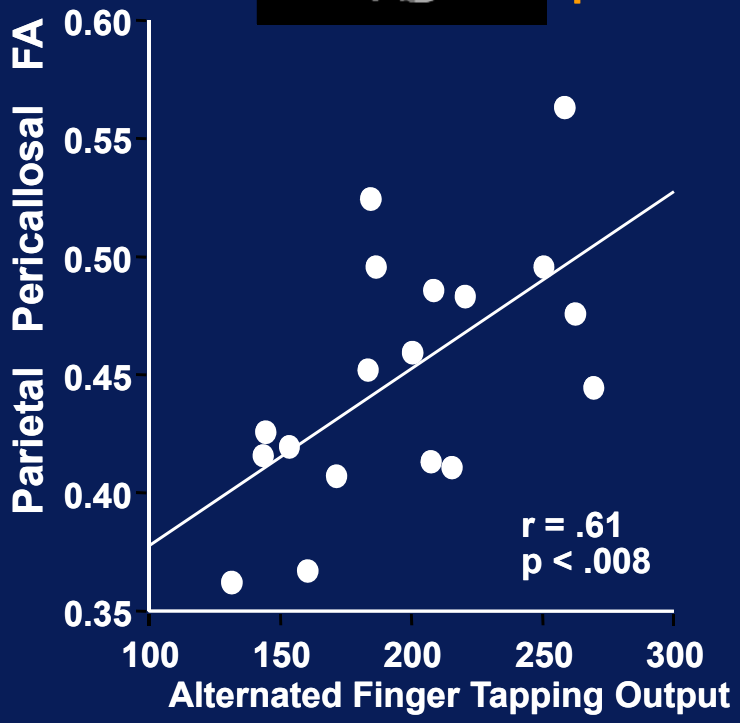
- Imaging brain white matter in normal aging
  - Macrostructural volumes
  - Microstructural constituents
  - Genetic contribution to structure
- White matter integrity and function in age
- White matter integrity and function in alcoholism
- White matter integrity and connectivity

FA and Alternated Finger Tapping

Interhemispheric Transfer Test



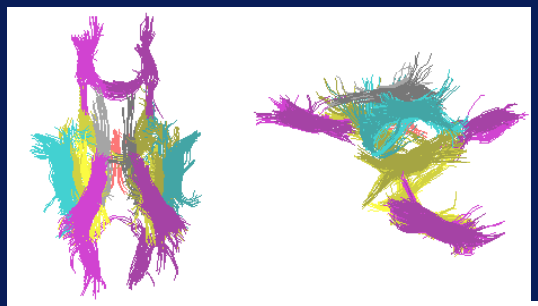


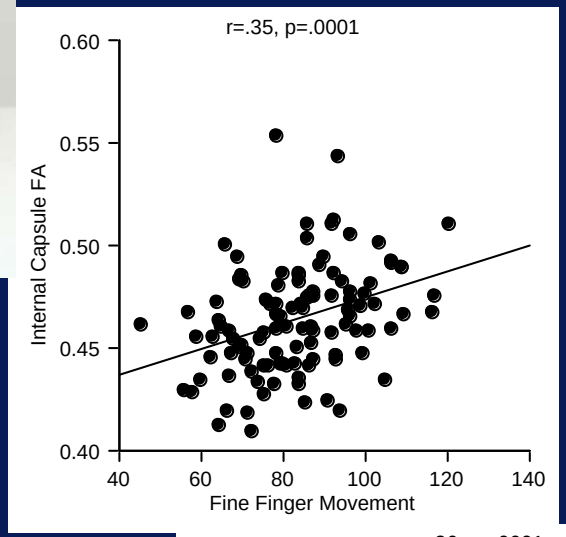


Sullivan et al. *NeuroReport* 2000

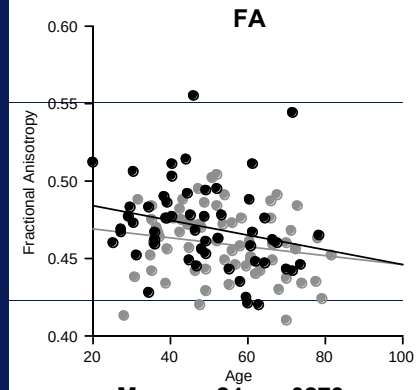
Internal Capsule Sample and Age

Fine Finger Movement

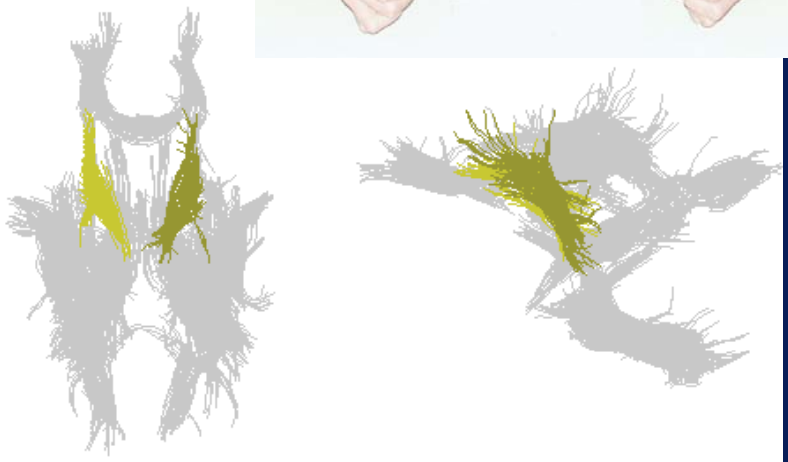


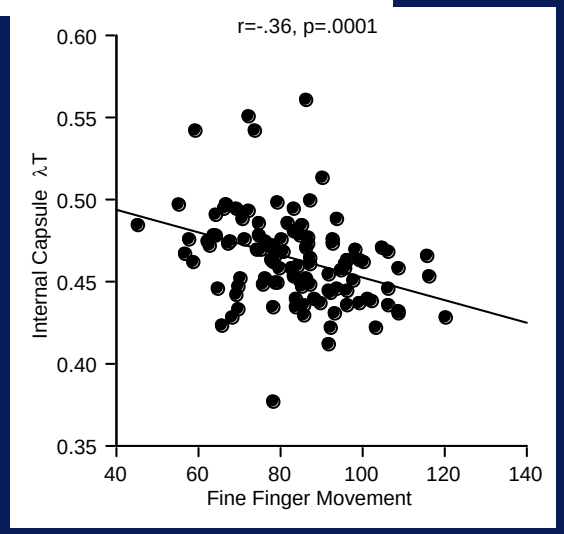


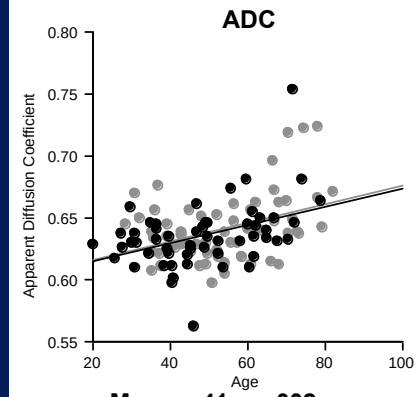
Internal Capsule



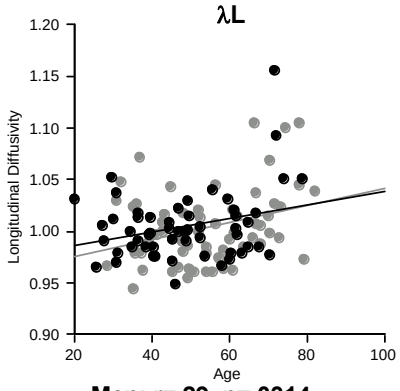
Men: r=-.24, p=.0273
Women: r=-.18, p=.15



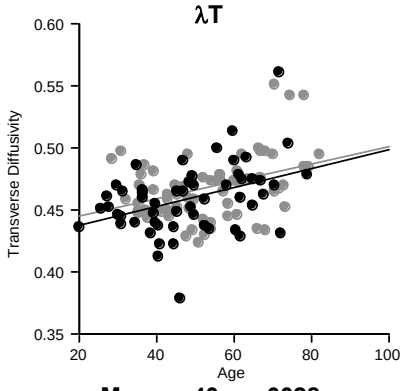




Men: r=.41, p=.002
Women: r=.39, p=.0015



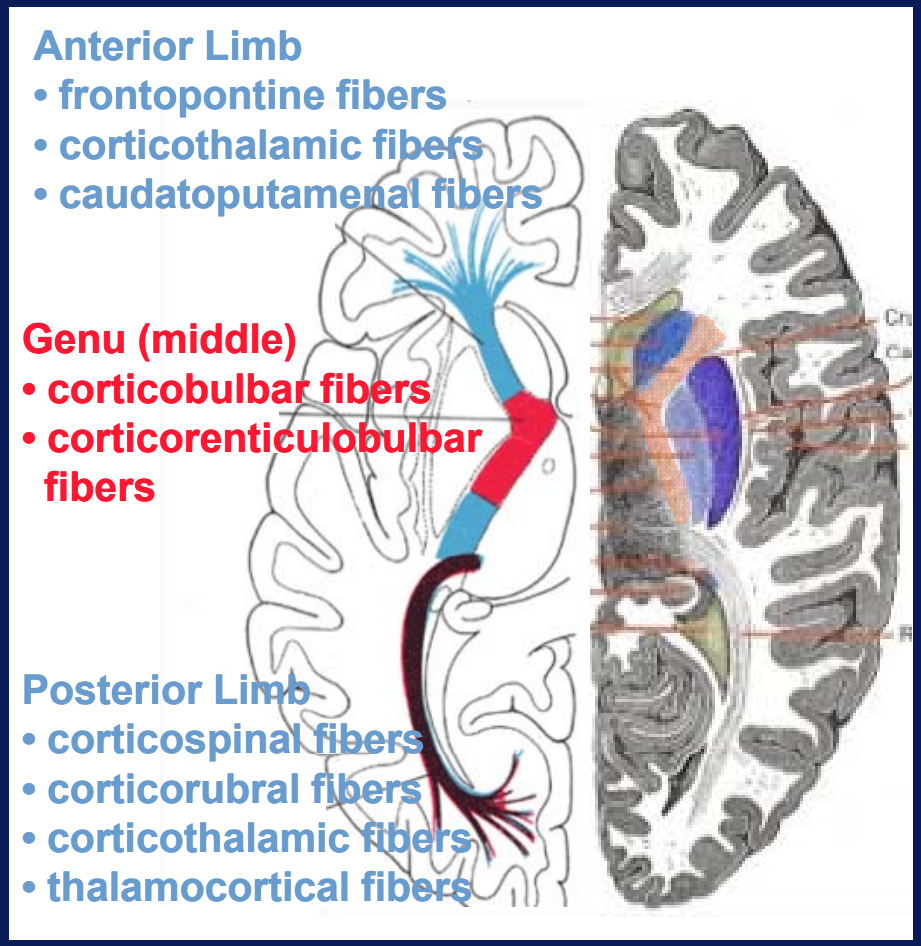
Men: r=.29, p=.0314
Women: r=.32, p=.0103



Men: r=.40, p=.0028
Women: r=.37, p=.0023

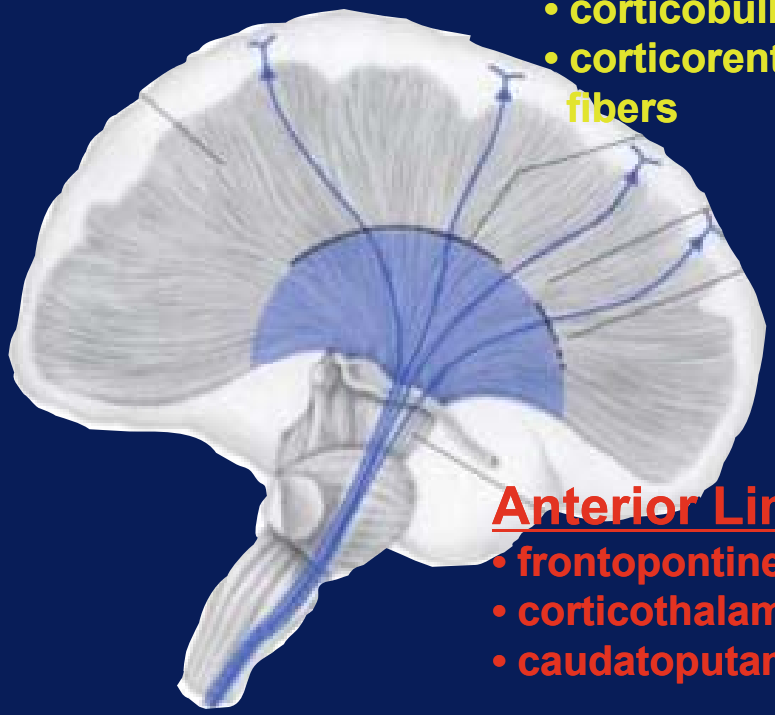
Sullivan et al.
***Neurobiology of Aging* 2010**

Internal Capsule
Topological Organization



Posterior Limb
- corticospinal fibers
- corticorubral fibers
- corticothalamic fibers
- thalamocortical fibers

Genu (middle)
- corticobulbar fibers
- corticorenticulobulbar fibers



Anterior Limb
- frontopontine fibers
- corticothalamic fibers
- caudatoputamenal fibers

Internal Capsule
Topological Organization

Anterior Limb
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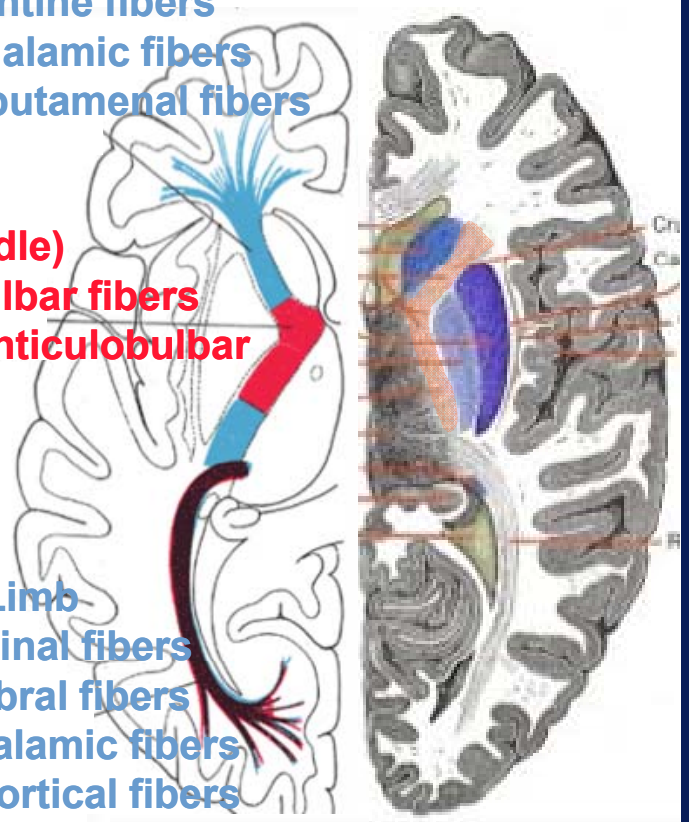
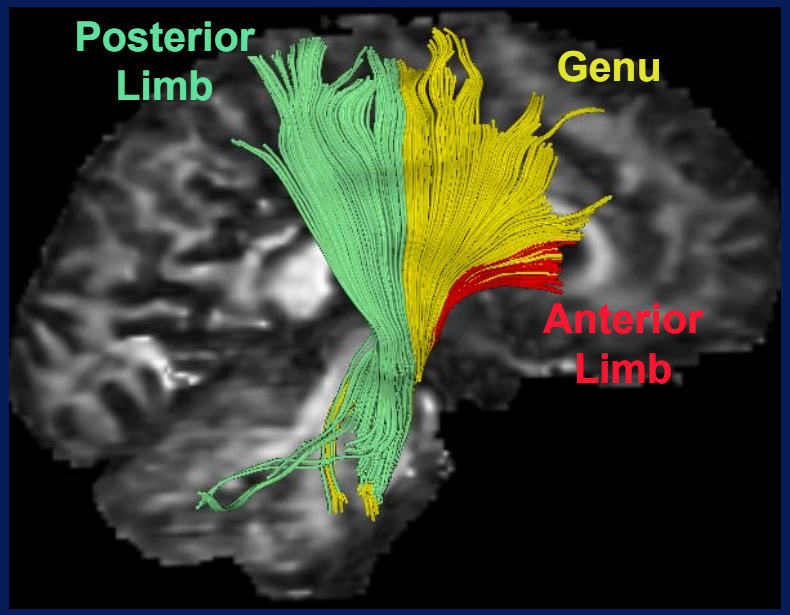
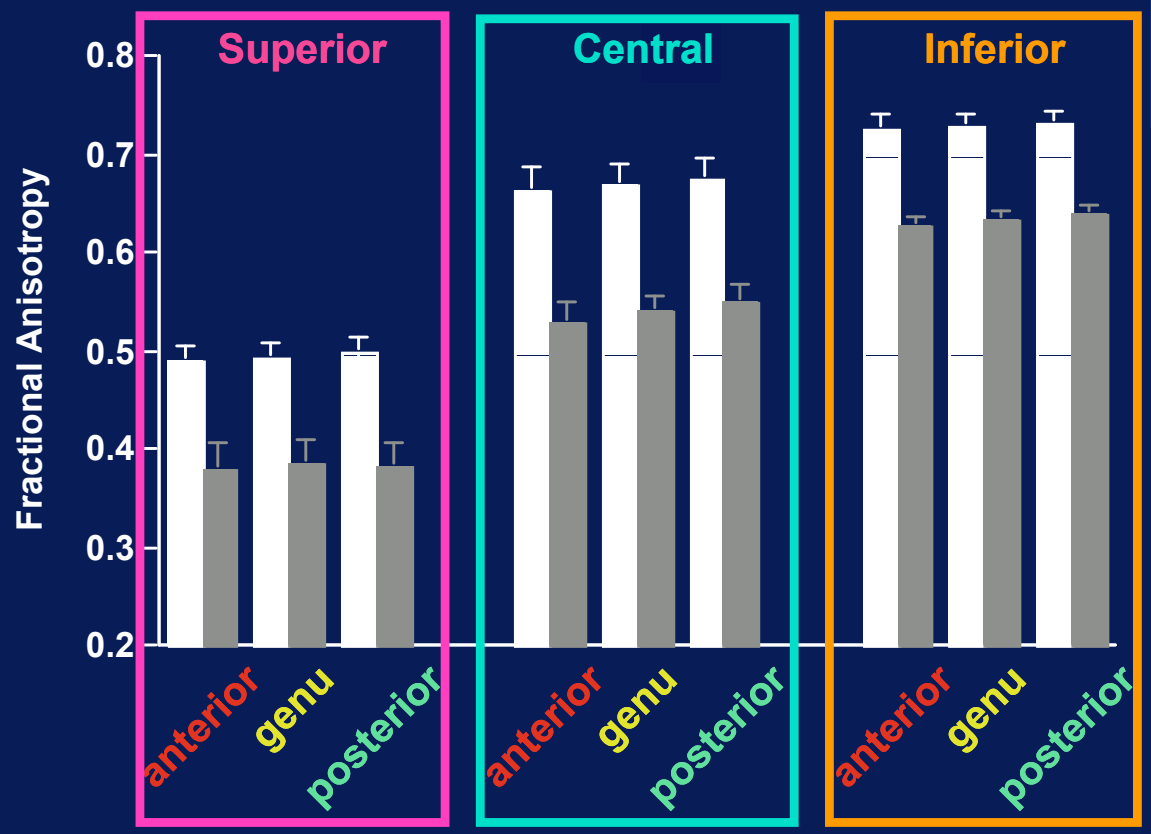


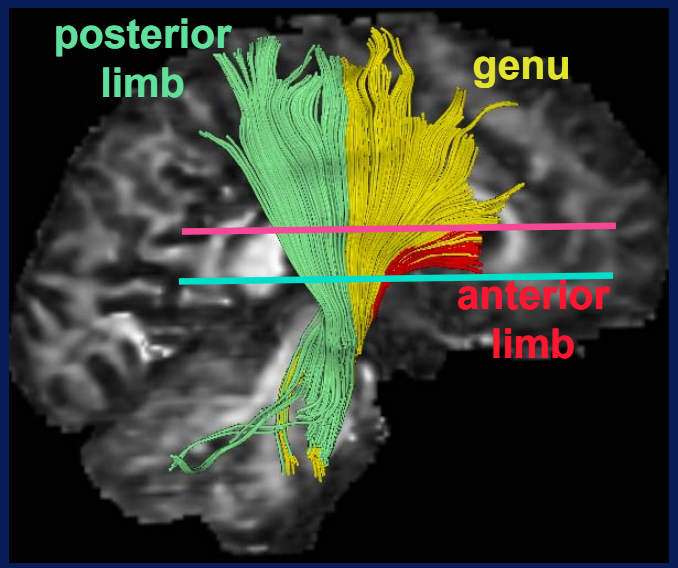


Internal Capsule Tracts

Fractional Anisotropy



	AGE	ED	NART IQ
Young (N=12)	26	16	114
Elderly (N=12)	78	17	118



Superior: Young > Elderly (p=.0006), no group x A-P interaction

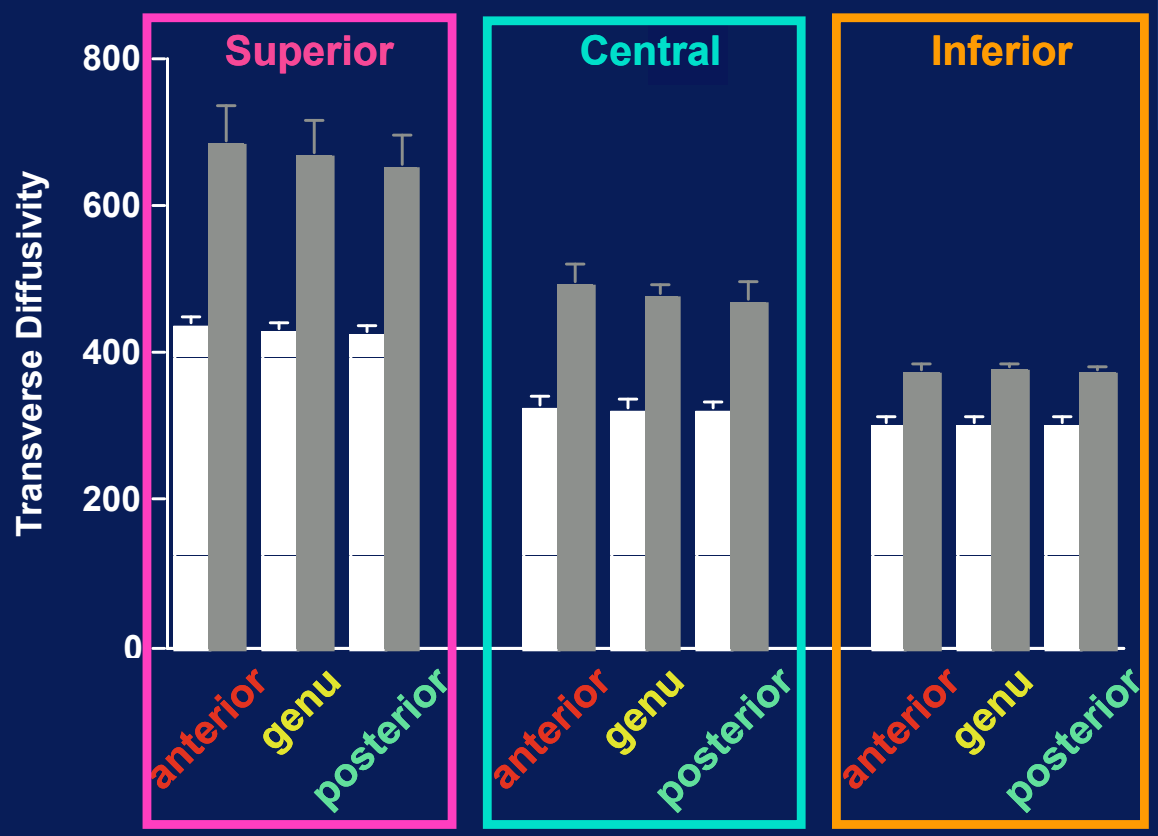
Central: Young > Elderly (p=.0001), no group x A-P interaction

Inferior: Young > Elderly (p=.0001), no group x A-P interaction

Sullivan, Zahr, Rohlfing, Pfefferbaum
***Neuropsychologia* 2010**

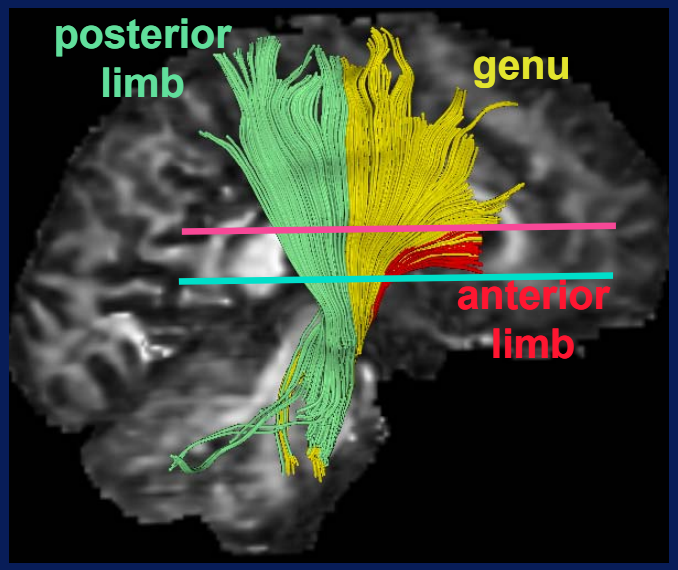
Internal Capsule Tracts

Transverse (λT) Diffusivity



Young (N=12)

Elderly (N=12)



Superior: Young < Elderly (p=.0001), no group x A-P interaction

Central: Young < Elderly (p=.0001), group x A-P interaction trend (p=.0917)

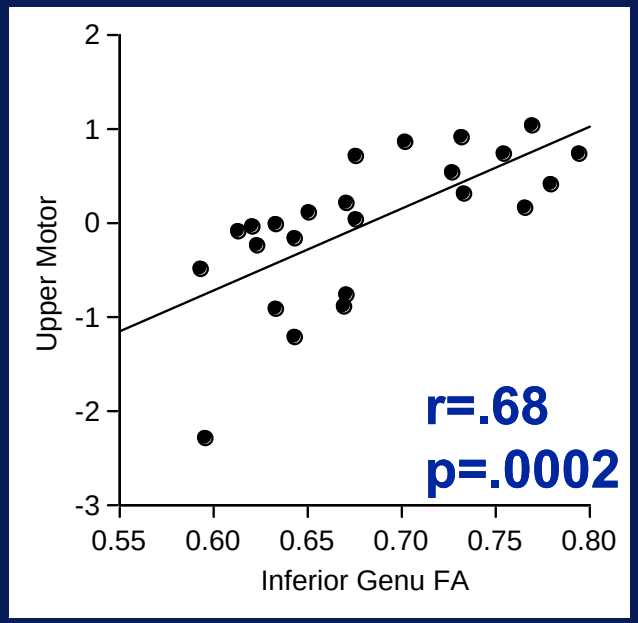
Inferior: Young < Elderly (p=.0001), no group x A-P interaction

Sullivan, Zahr, Rohlfing, Pfefferbaum
Neuropsychologia 2010

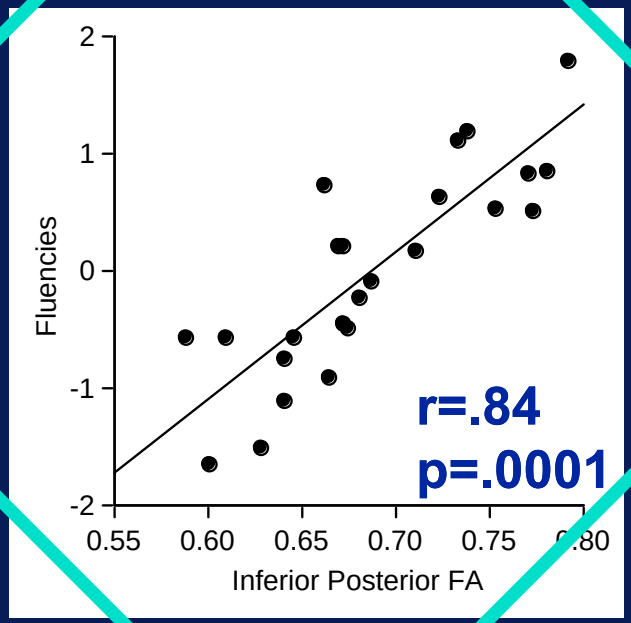
Internal Capsule and Performance

Fractional Anisotropy

Upper Limb



Fluencies



Damage to internal capsule

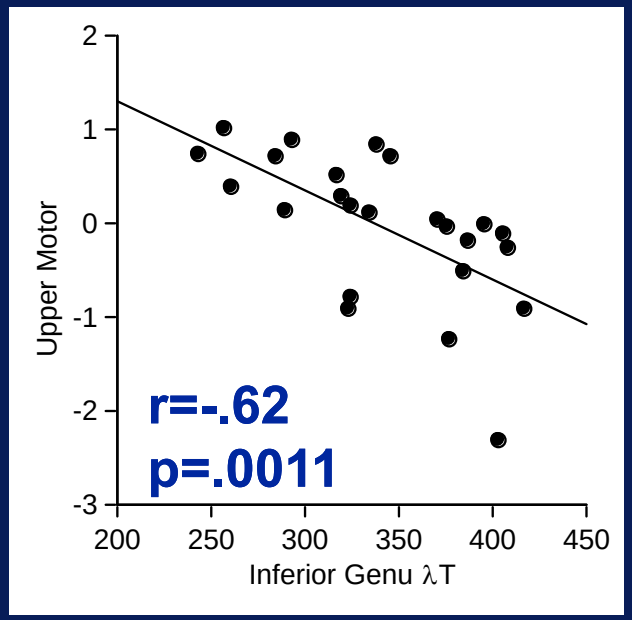
- **amotivation to speak**
- **facial and lingual weakness**

Sullivan, Zahr, Rohlfing, Pfefferbaum
***Neuropsychologia* 2010**

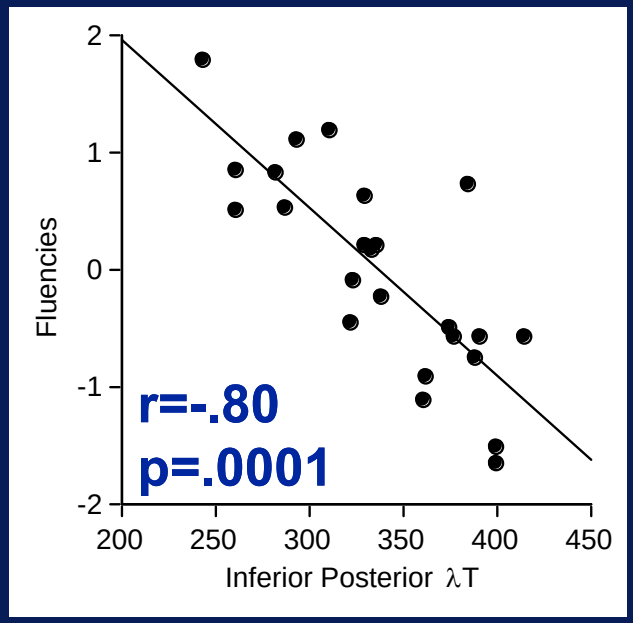
Internal Capsule and Performance

Transverse (□T) Diffusivity

Upper Limb



Fluencies



Sullivan, Zahr, Rohlfing, Pfefferbaum
Neuropsychologia 2010

White Matter Integrity
Age, Alcoholism, and Function

- Imaging brain white matter in normal aging
  - Macrostructural volumes
  - Microstructural constituents
  - Genetic contribution to structure
- White matter integrity and function in age
- White matter integrity and function in alcoholism
- White matter integrity and connectivity

Alcohol Dependence: DSM-IV

- Maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, manifested by 3 or more of the following in a 12-month period:
  - Tolerance
  - Withdrawal
  - Increasing consumption
  - Unsuccessful in cutting down
  - Inordinate time spent obtaining alcohol
  - Marked deterioration in life activities
  - Continued use despite physiological or psychological problems

12.5% men, 1.5% women lifetime prevalence of alcohol dependence

Alcoholism: Common and Costly

- 7 to 10% of U.S. adult population
- 14 to 20% of admissions to private hospitals
- 30 to 35% entering university or municipal teaching hospitals
- 50% of those being treated in VA medical, surgical, and psychiatric inpatient facilities

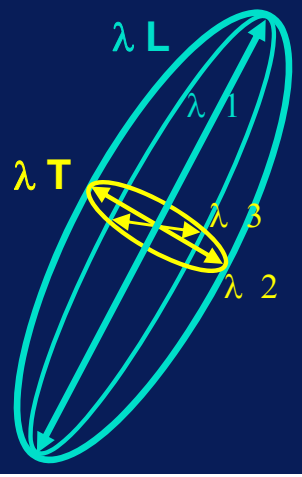
- **About 1/3 to 1/2 of treatment-seeking alcoholics have detectable cognitive or motor impairments.**

Arciniegas and Beresford
Neuropsychiatry: An Introductory Approach 2001

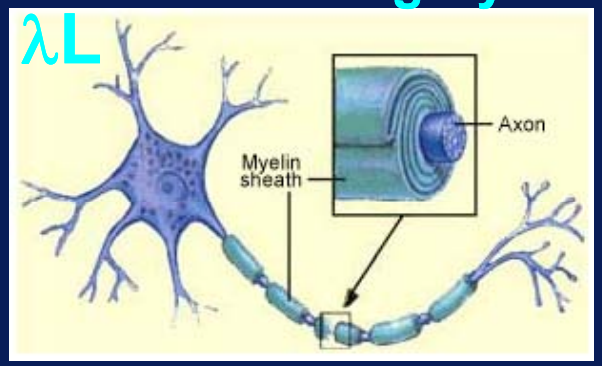
Alcoholism and White Matter

- **In vivo studies**
  - White matter = gray matter volume shrinkage
- **Postmortem studies**
  - White matter more affected than gray matter
  - Demyelination
  - Microtubule disruption
  - Axonal deletion
  - Notable in frontal regions

⇨ ***DTI quantification of FA and diffusivity components***

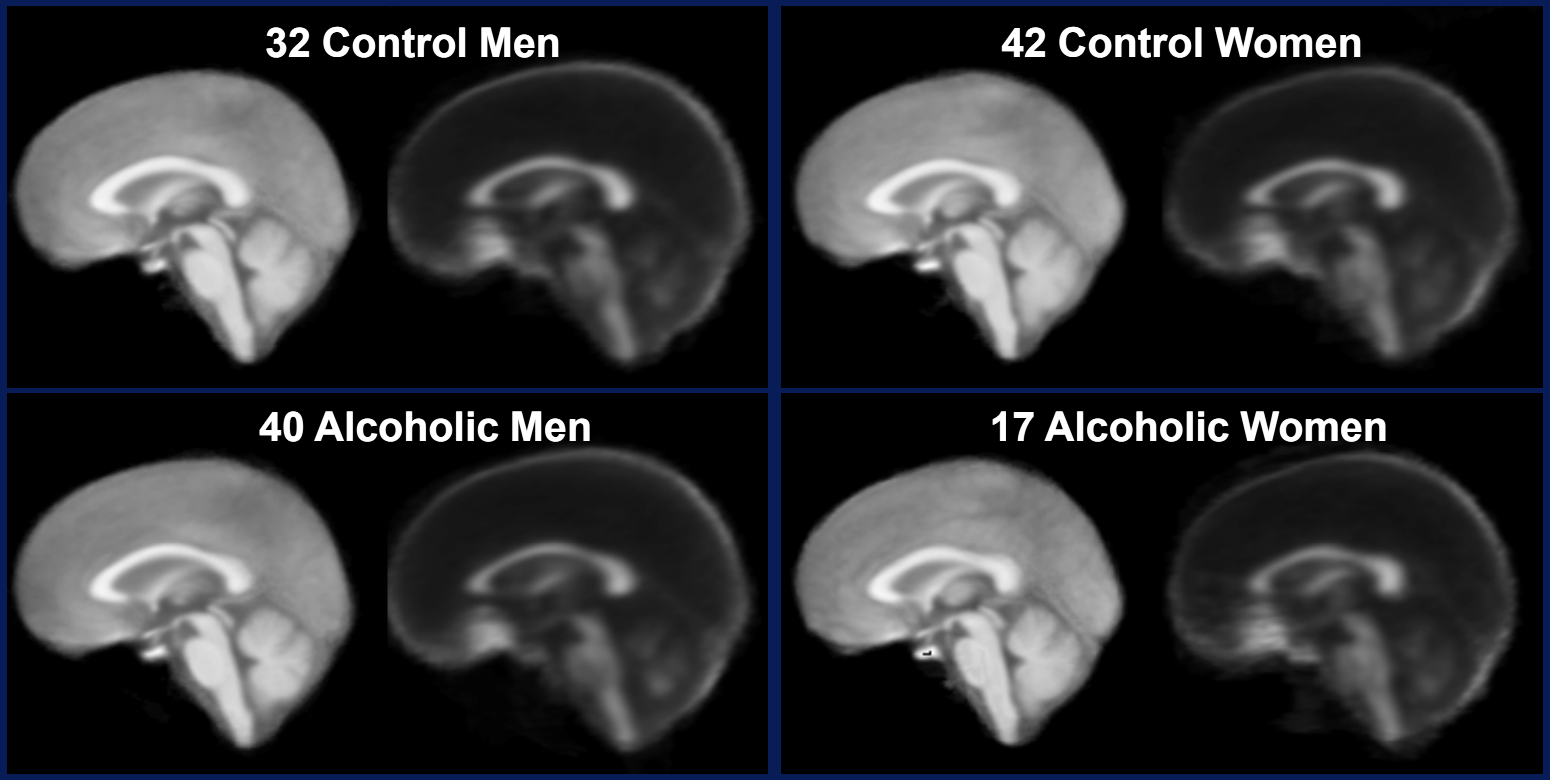


Axonal integrity



Myelin integrity

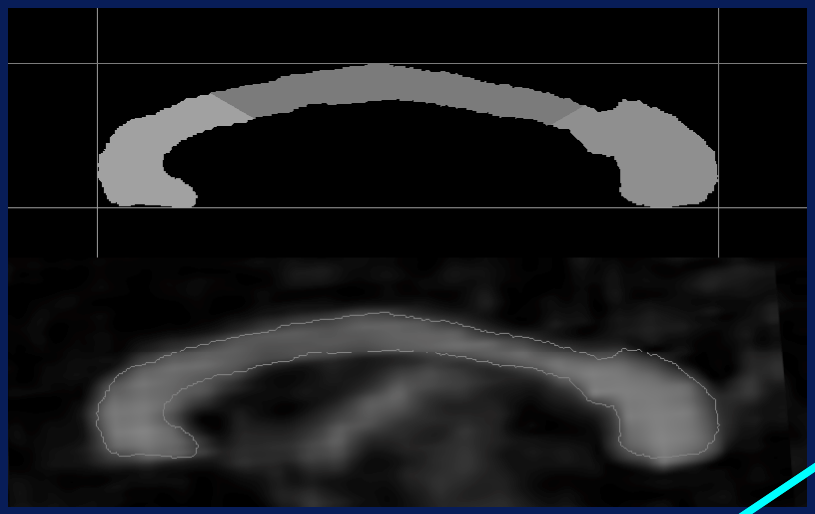
Alcoholism and White Matter FA



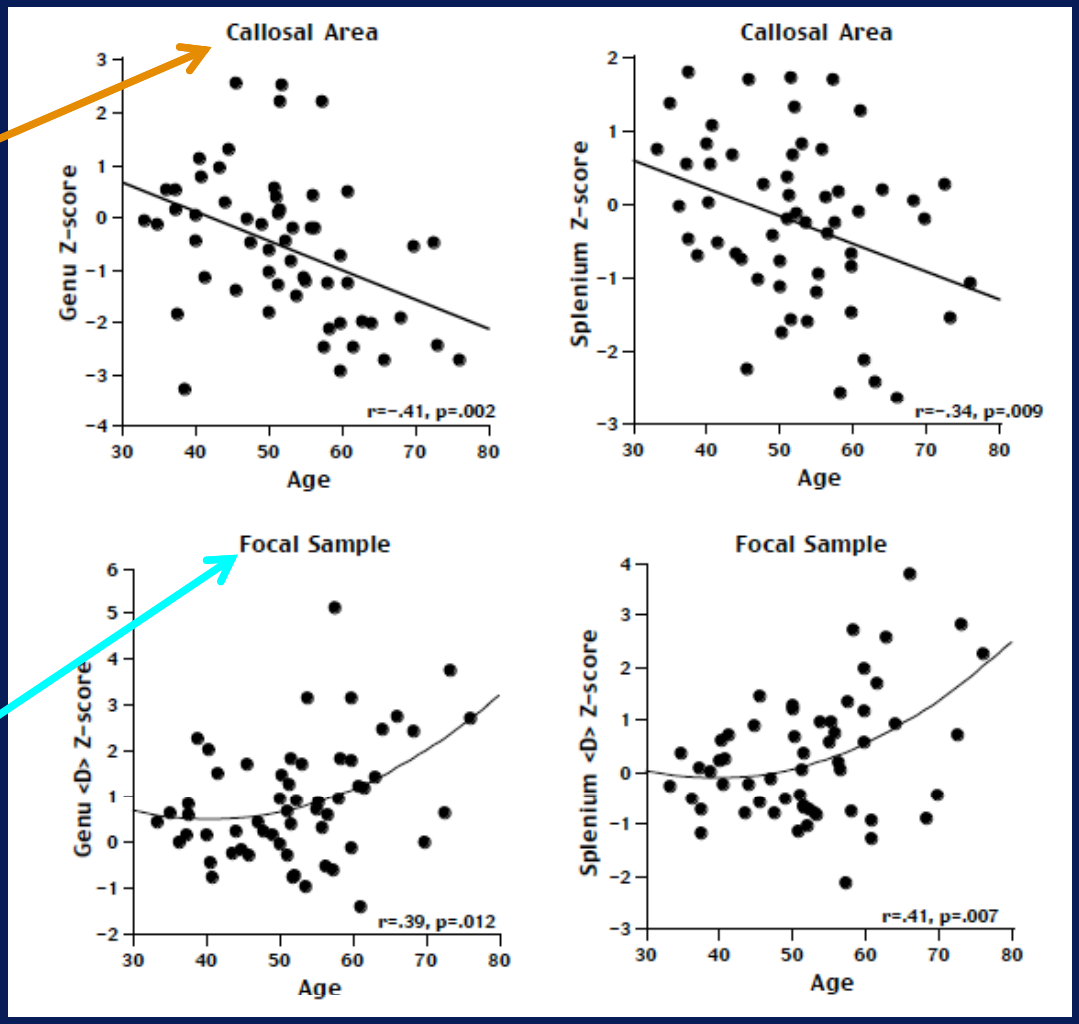
Pfefferbaum, Adalsteinsson & Sullivan
Biological Psychiatry 2006

Age-Alcoholism Interaction

Callosal size



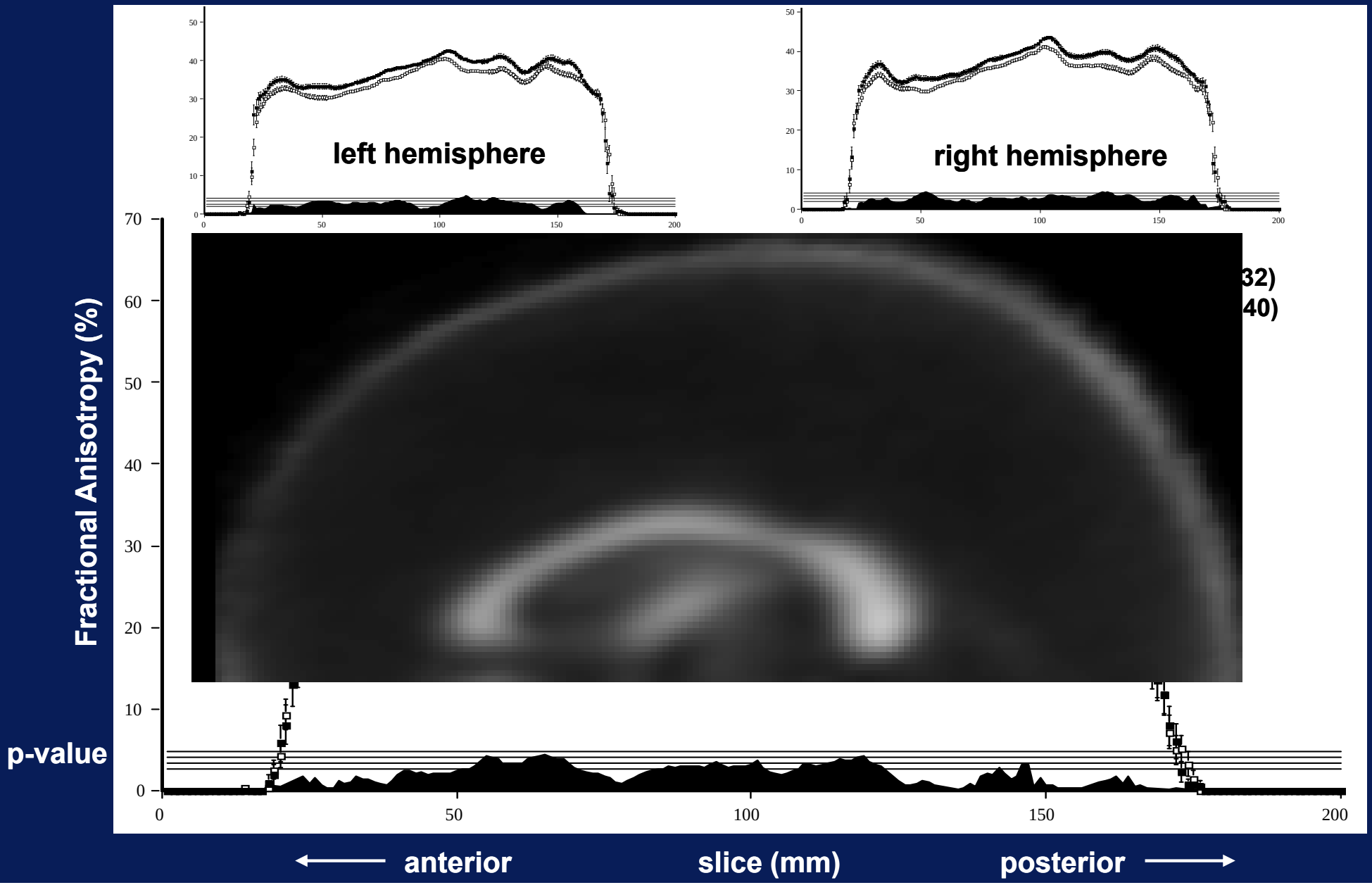
Callosal diffusivity



Pfefferbaum et al. *Neurobiology of Aging* 2006

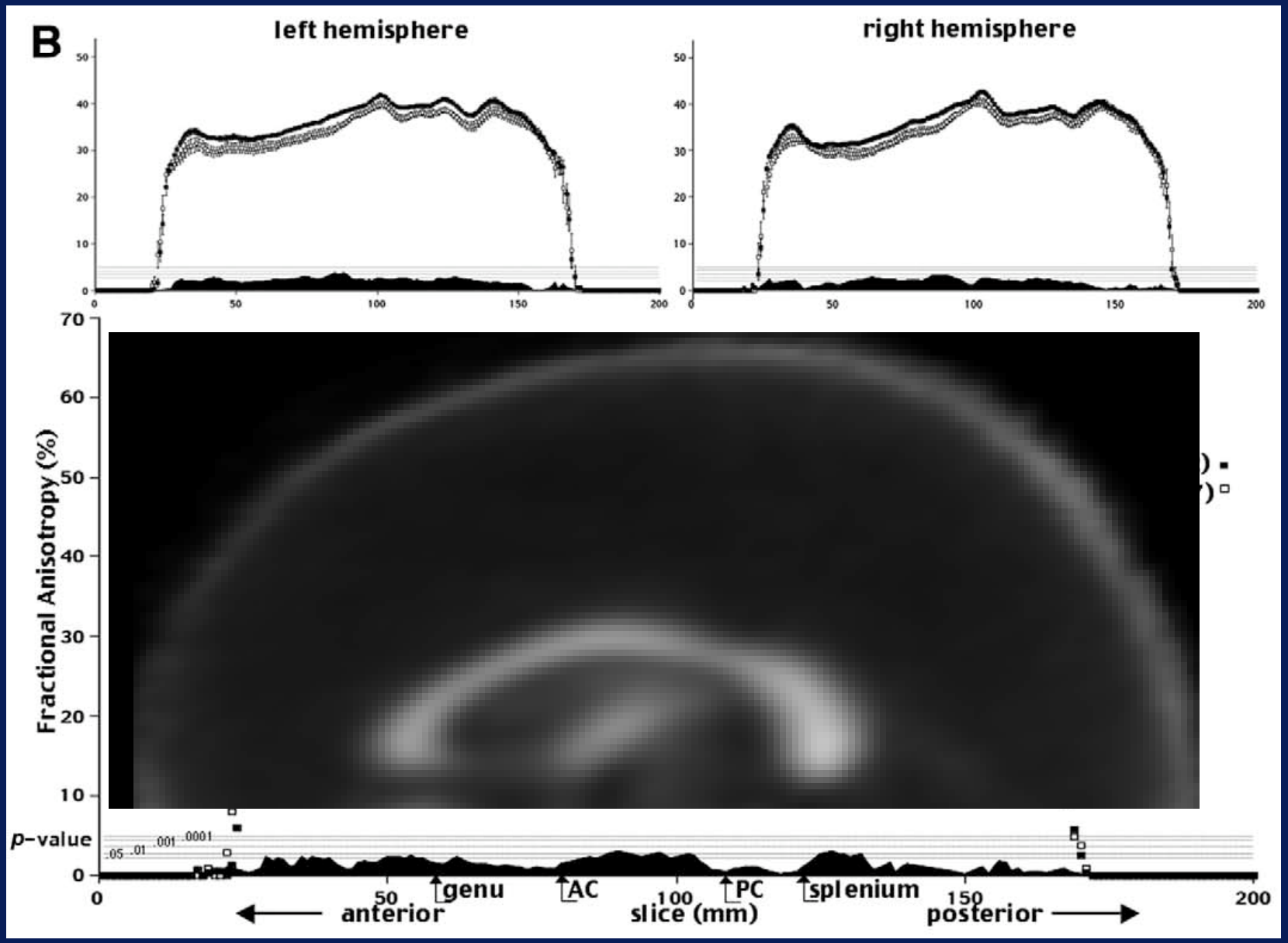
Pfefferbaum, Adalsteinsson & Sullivan
Biological Psychiatry 2006

Distribution of Alcoholism's Effects on FA of White Matter in Men



Pfefferbaum, Adalsteinsson & Sullivan
Biological Psychiatry 2006

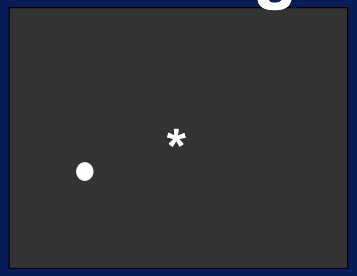
Distribution of Alcoholism's Effects on FA of White Matter in Women



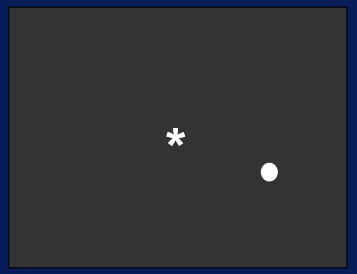
Redundant Targets Effect

Callosal Integrity and Alcoholism

Single Stimuli

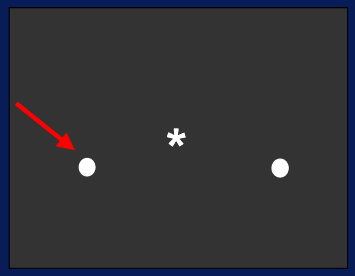


S1: left

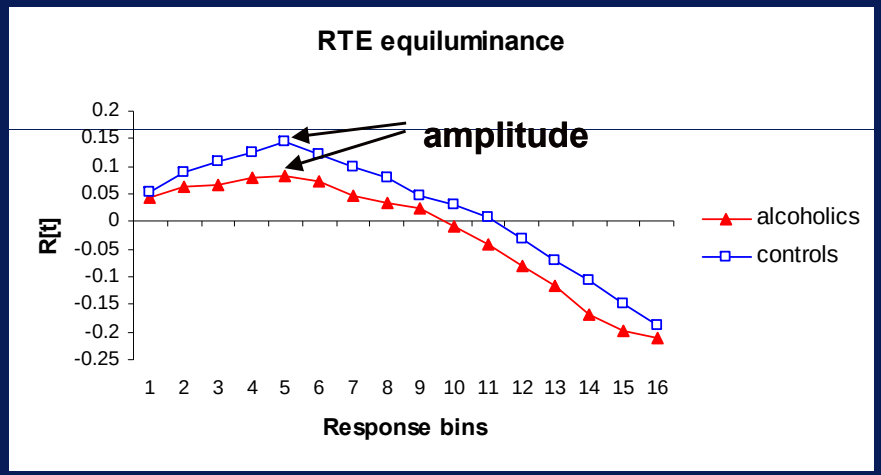


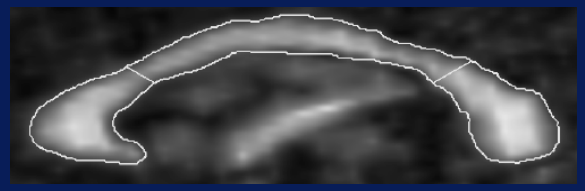
S2: right

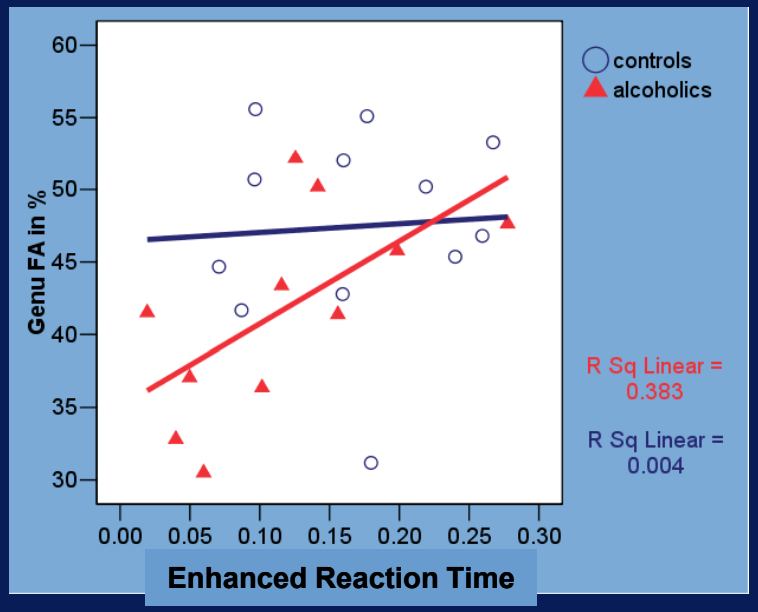
Paired Stimuli



S1S2: left + right bilateral







Schulte, Pfefferbaum, Sullivan *Neuropsychologia* 2004
Schulte et al. *Cerebral Cortex* 2005
Schulte et al. *NeuroImage* 2006

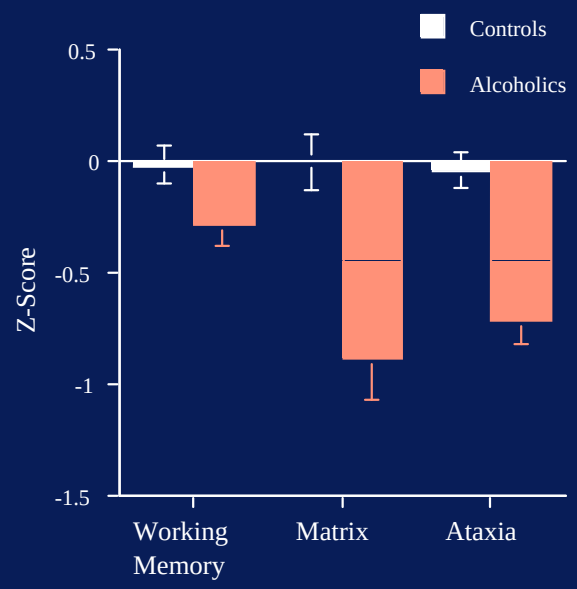
Pfefferbaum, Adalsteinsson & Sullivan
Neurobiology of Aging 2006

Selective Relationships

Callosal Regions and Cognition in Alcoholics

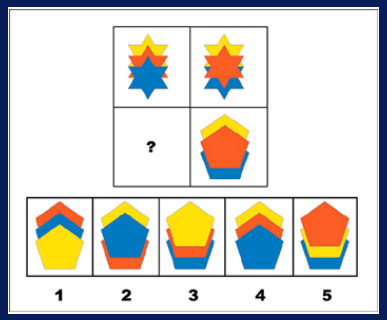
- **Working memory**

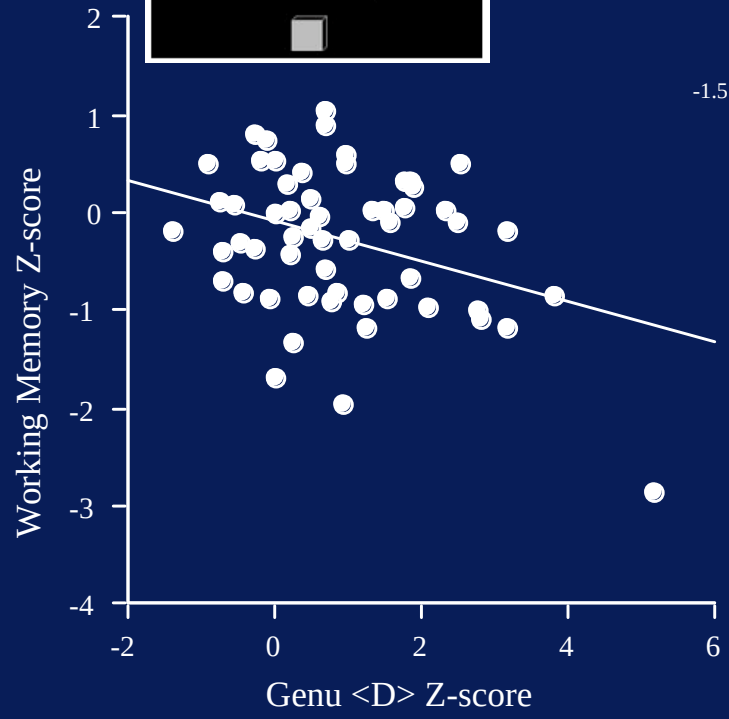
BACKWARD DIGIT SPAN
Hear: 3-7-2-8-1
Say: 1-8-2-7-3
BACKWARD BLOCK SPAN

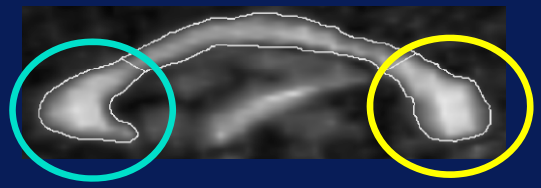


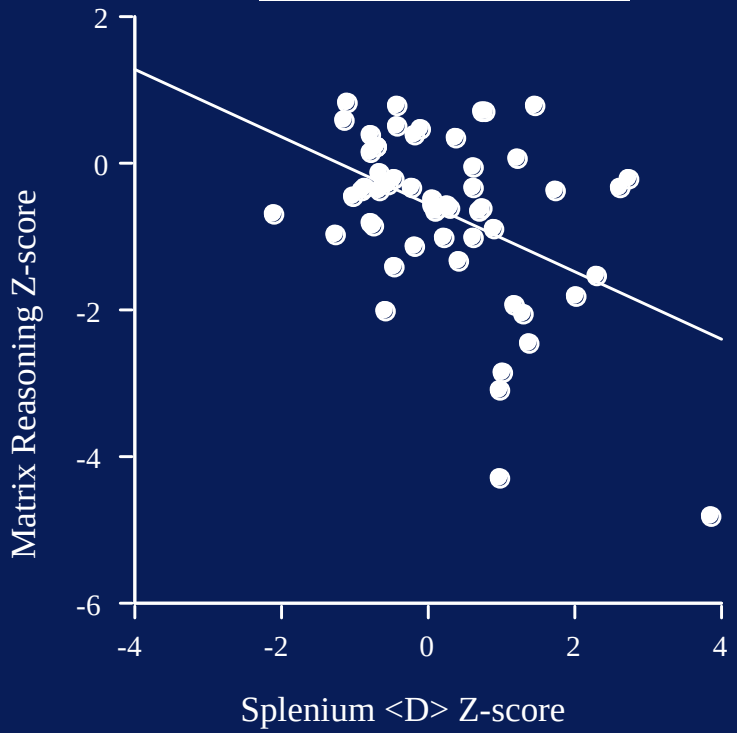
- **Visuospatial ability**

MATRIX REASONING









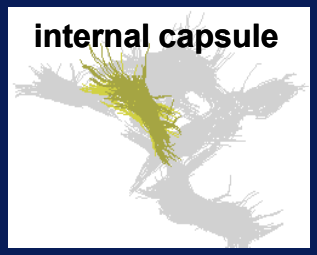
- Poor **working memory** relates to high

- Poor **matrix reasoning** relates to high **splenium** but not genu diffusivity

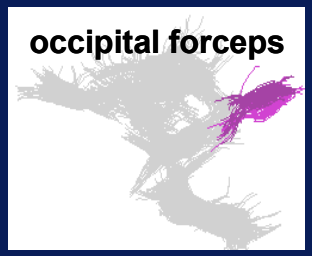
Regional White Matter Fiber Bundles

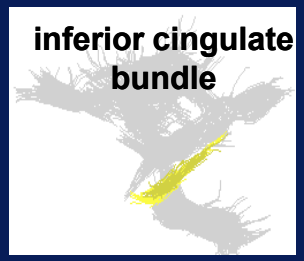
Alcoholism Pattern of Disruption

- Frontal and superior fibers are especially vulnerable



- Posterior and inferior fibers are relatively preserved

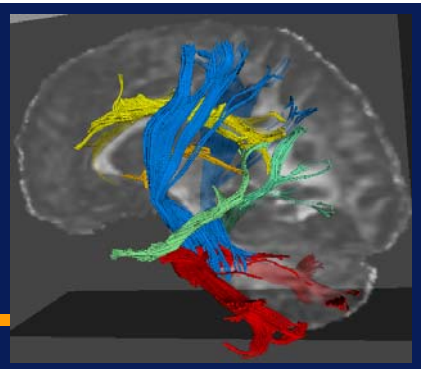




- FA and λT affected in alcoholic men
- λT affected in alcoholic women

Pfefferbaum et al. *Biological Psychiatry* 2009

SRI/Stanford Neuroscience Imaging Program



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