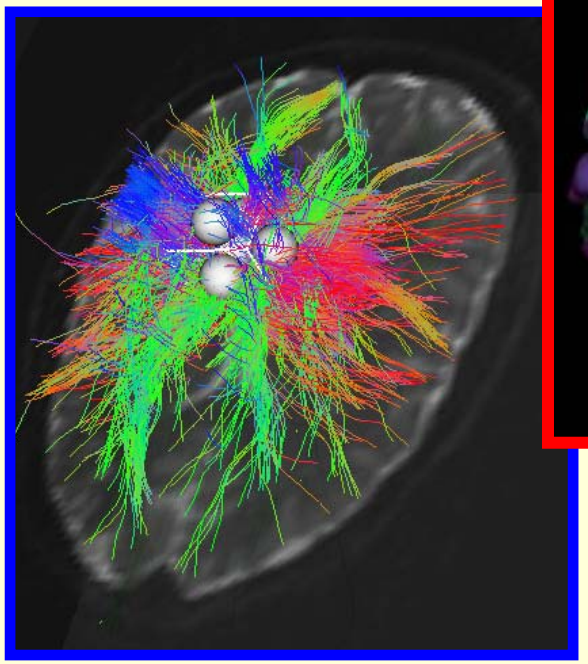
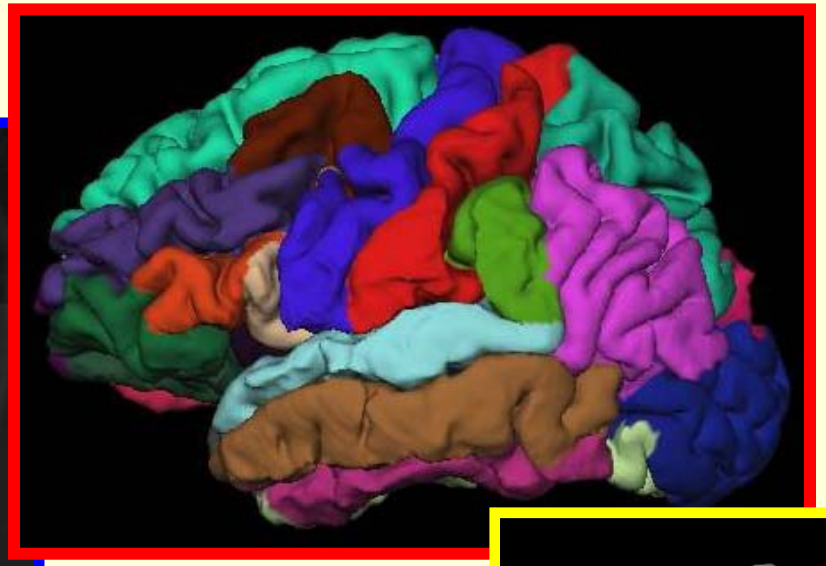
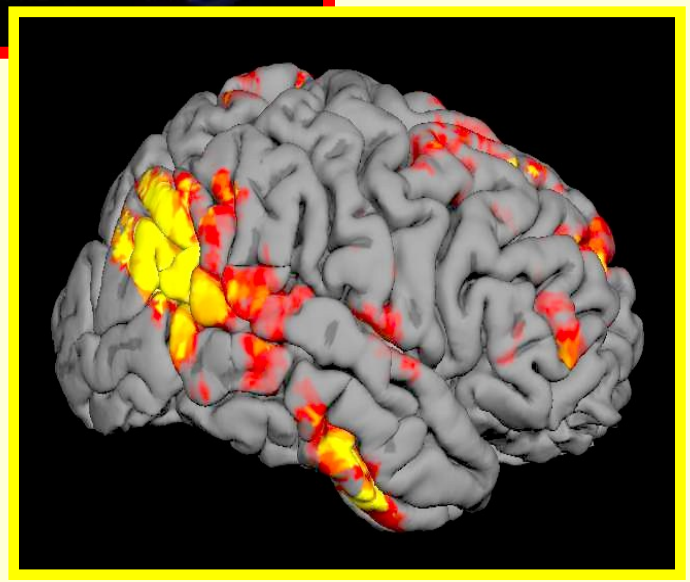
Neuroimaging the Aging Mind

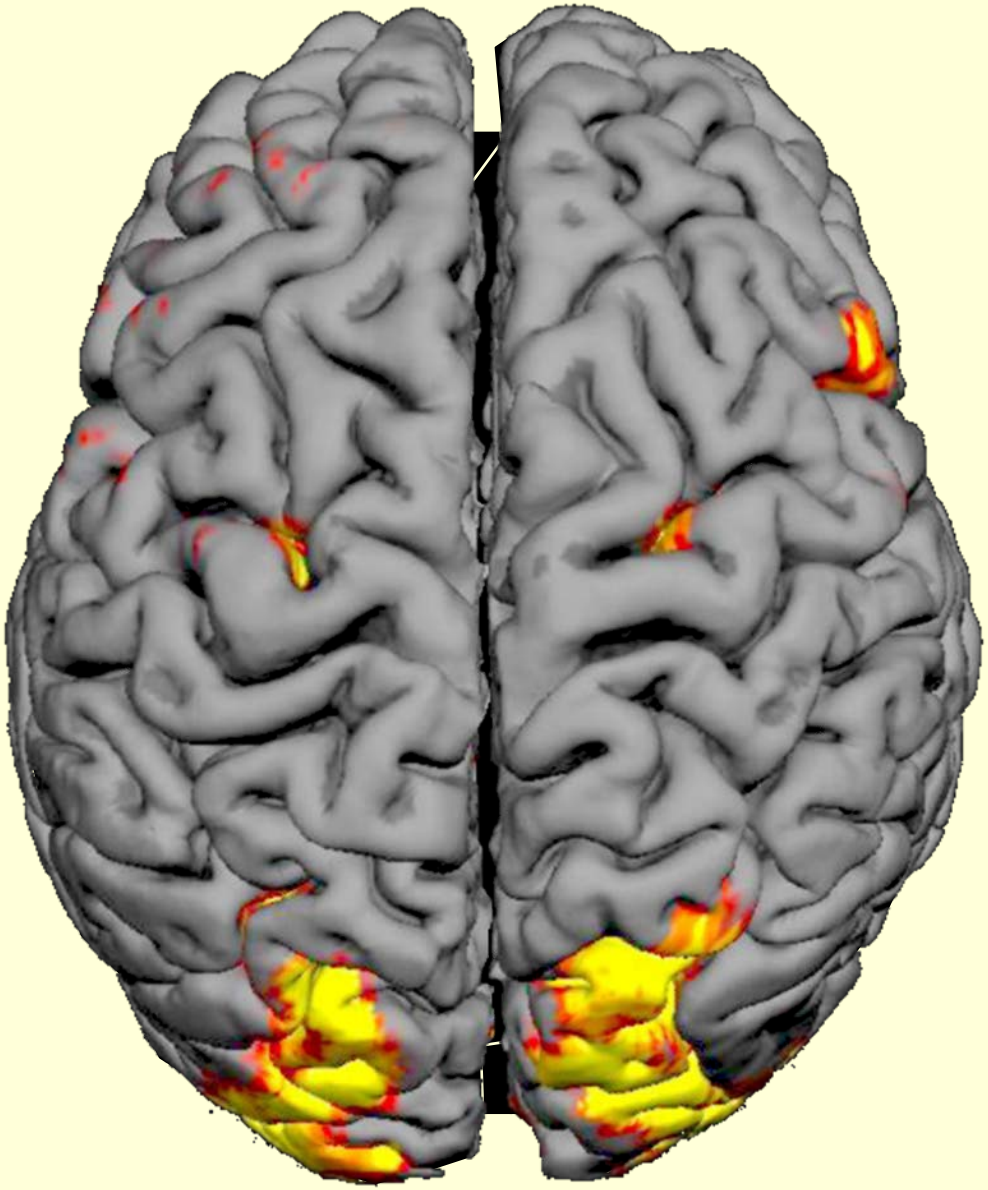






Scott Huettel

Duke University

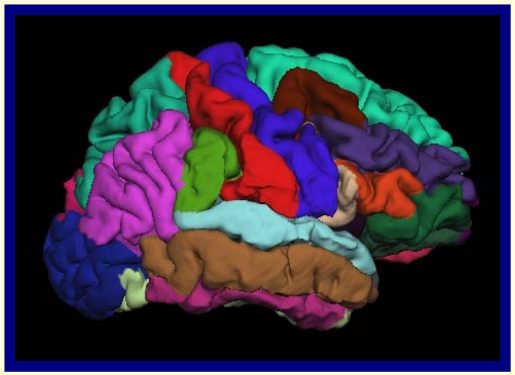


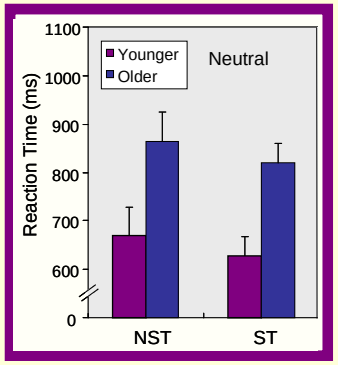
Major Themes: Methodology and Function

- Neuroimaging methods and aging
  - Brief introductions for non-specialists
  - Methodological challenges & caveats
- Insights from cognitive neuroscience
  - What not to do?! (… fortunately, simple)
  - Moving to *neural constructs*
- Summary and guidance

Neuroimaging the Aging Mind: Methods

- Structural MRI
  - MRI Volumetrics
  - Diffusion Tensor Imaging (DTI)
- Functional MRI (fMRI)
  - Hemodynamic issues
  - Task-related issues

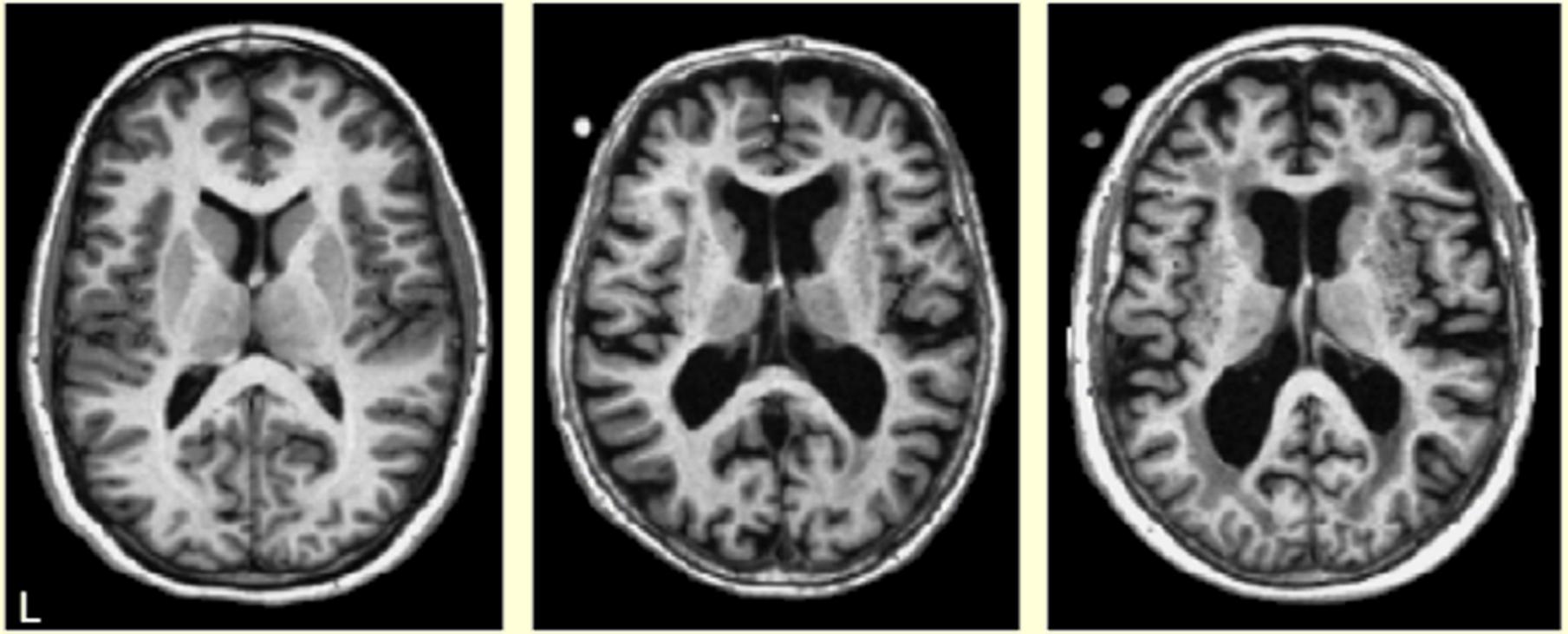




Younger Adult (19yo)

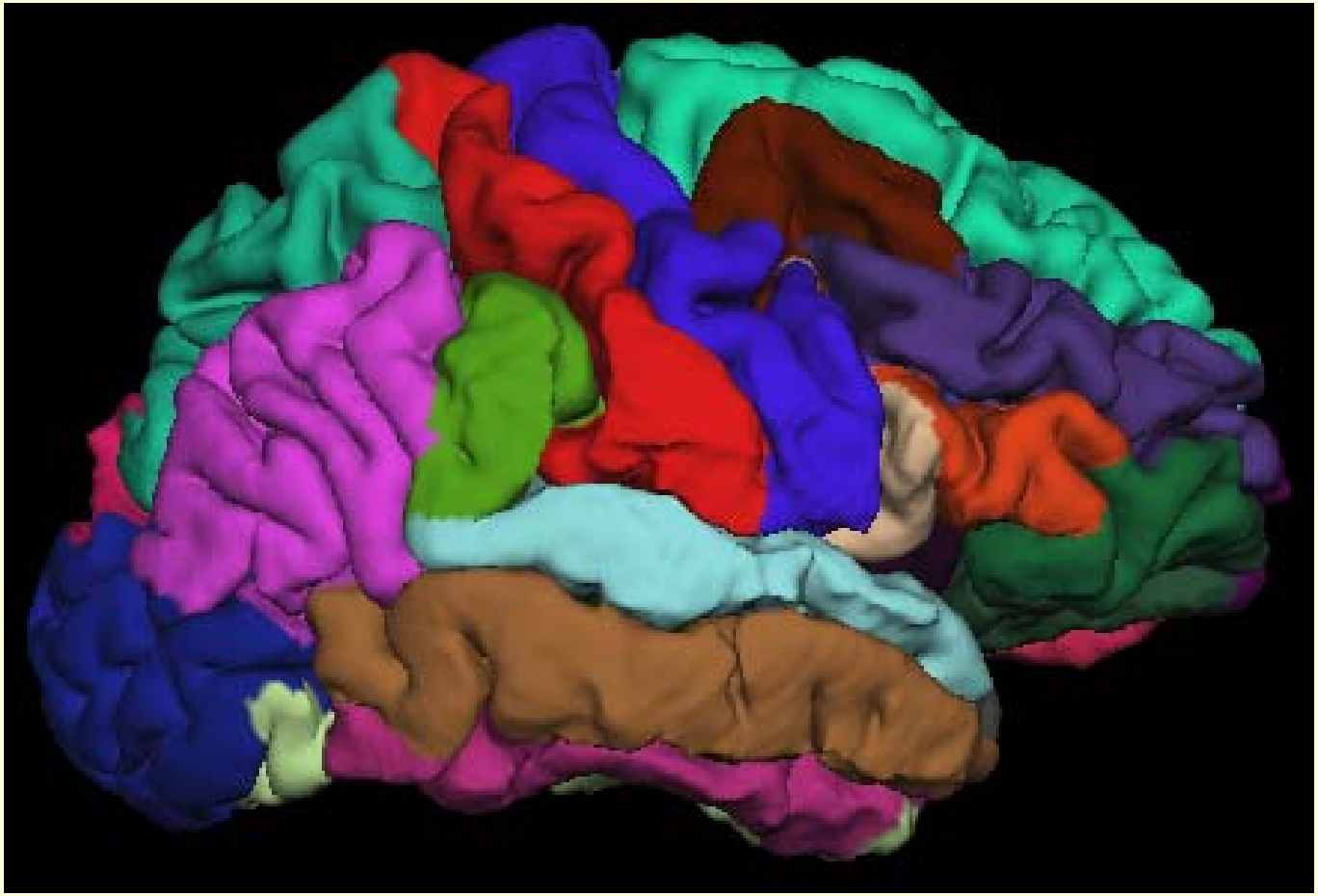
Healthy Older Adult (94yo)

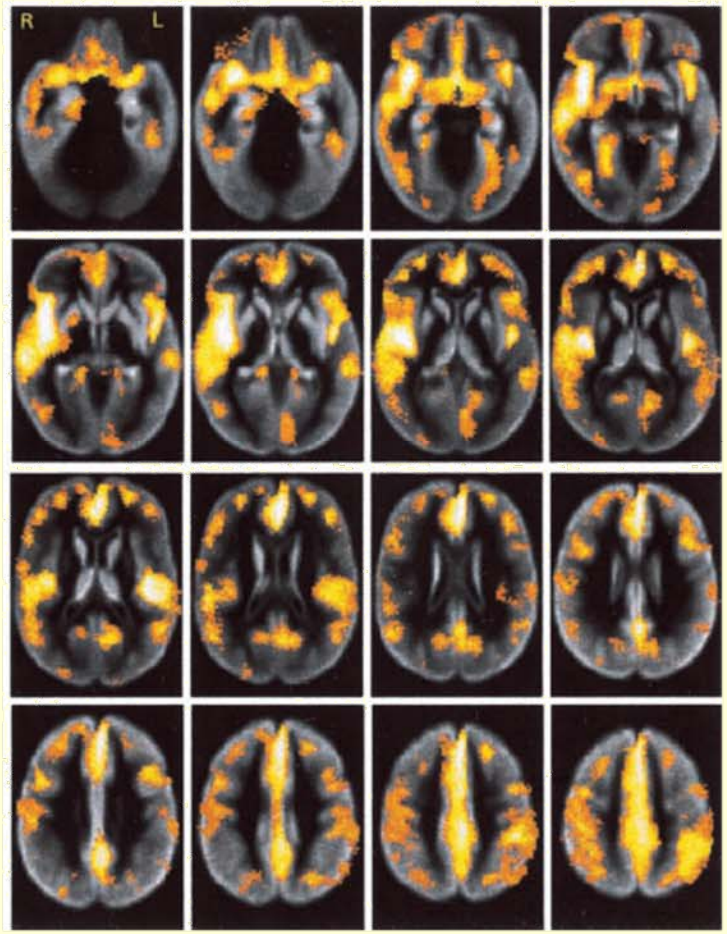
Older Adult w/dementia (77yo)



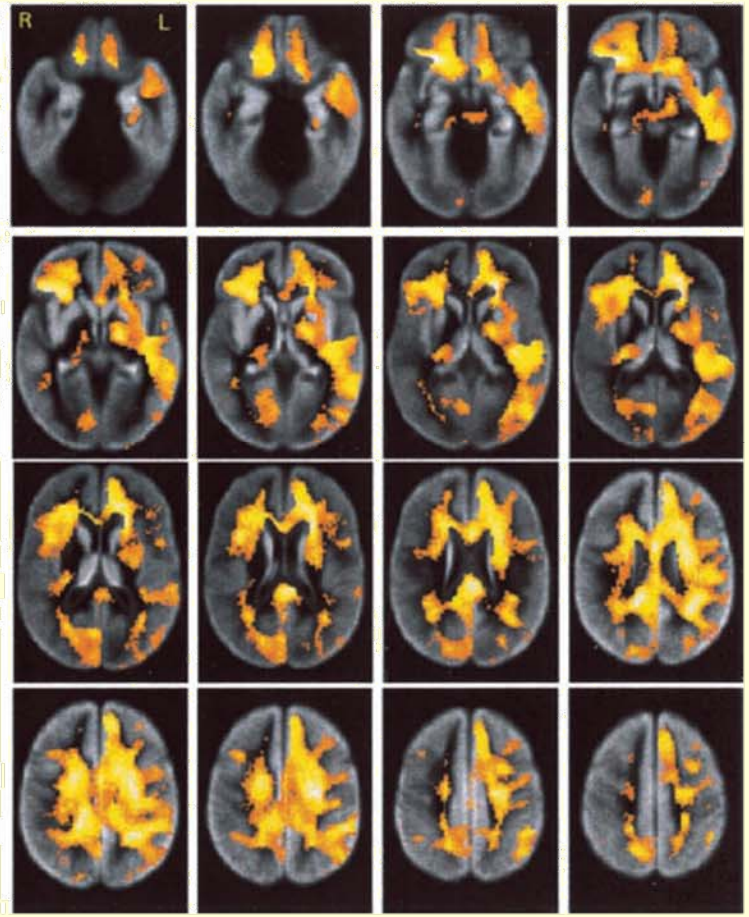
Buckner et al. (2004)

Morphometrics/Volumetrics





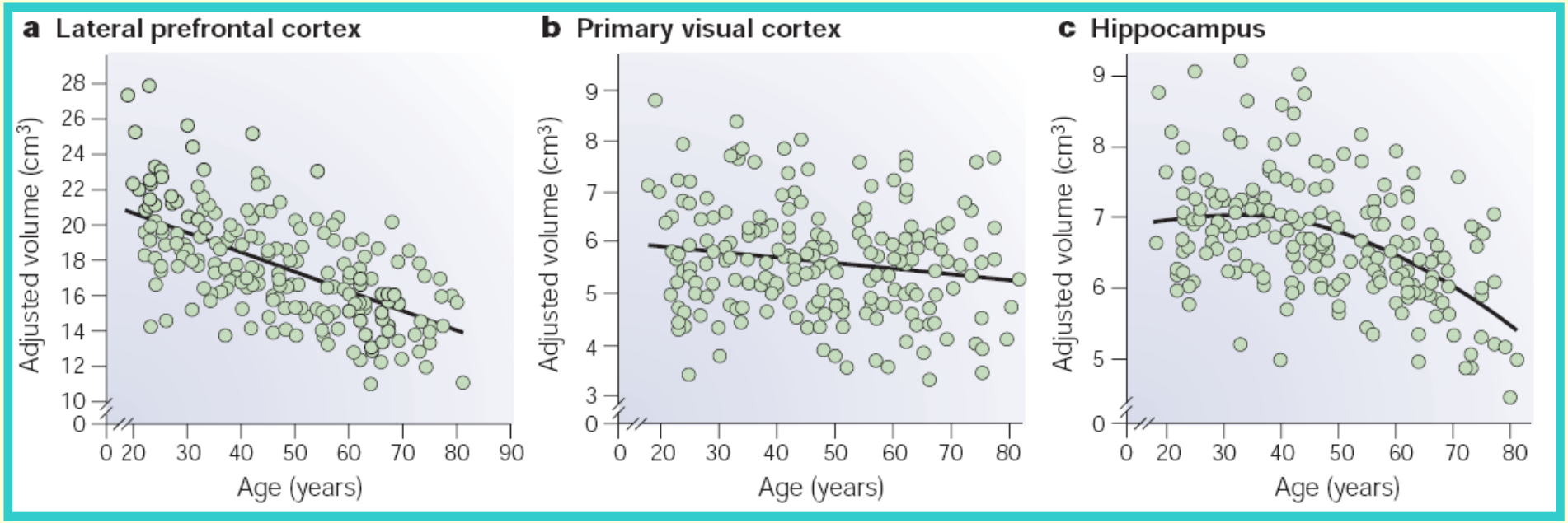
Gray Matter
(areas of decline over 4 years)



White Matter
(areas of decline over 4 years)

Resnick et al. (2003)

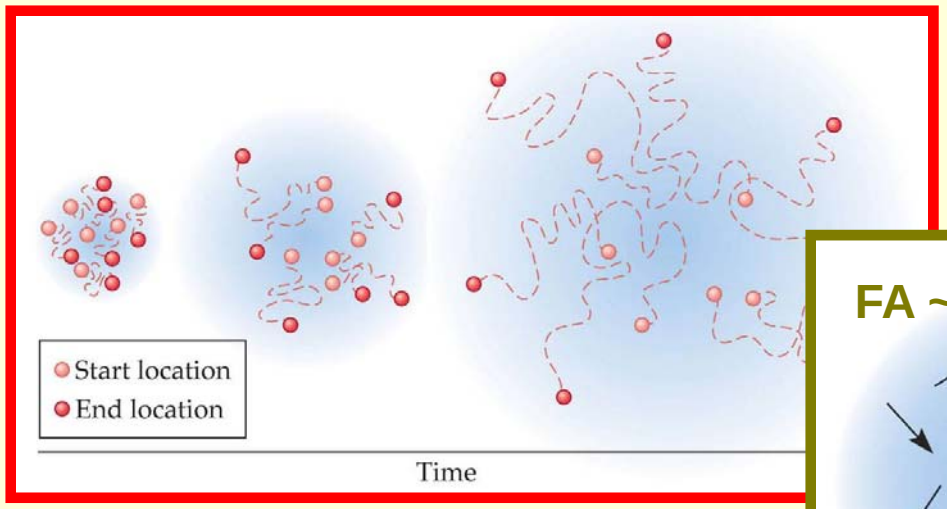
Gray Matter Changes over the Lifespan

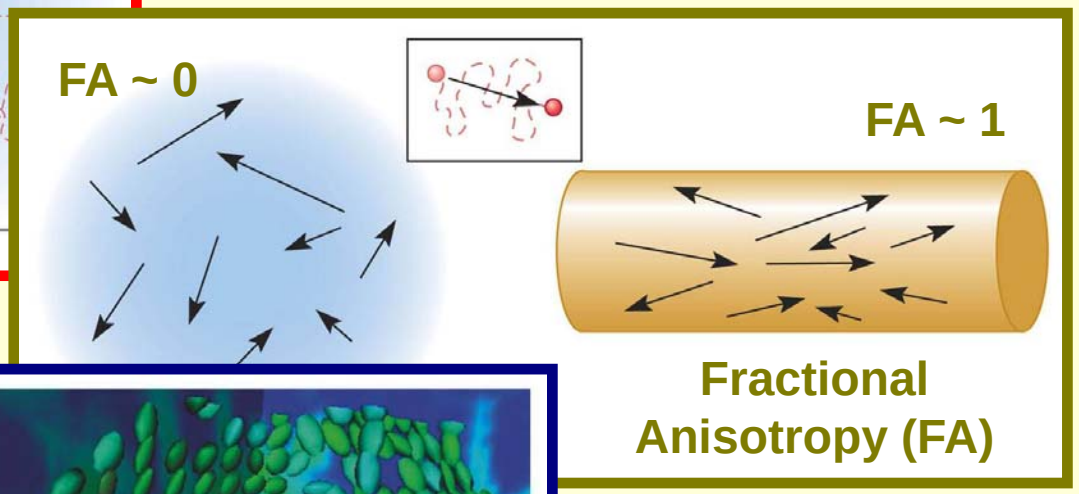


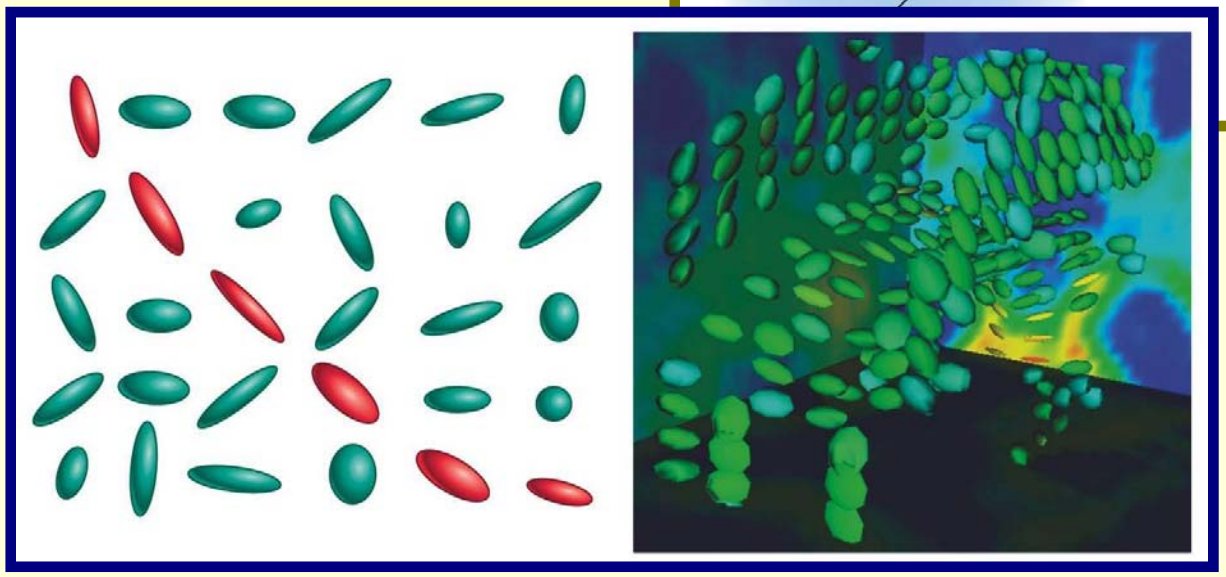
Data from Raz et al. (2004); figure from Hedden & Gabrieli (2004)

These effects are attributable primarily to loss of synaptic density (secondarily, to cell death).

Diffusion Tensor Imaging

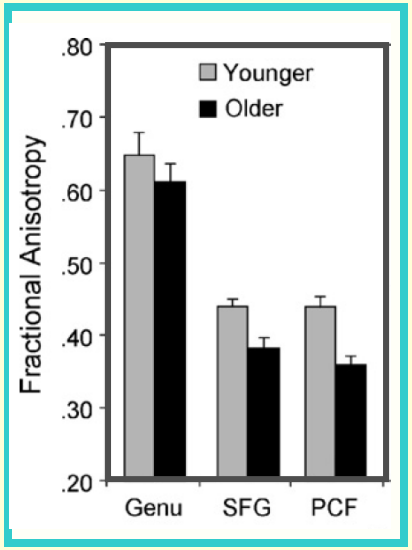


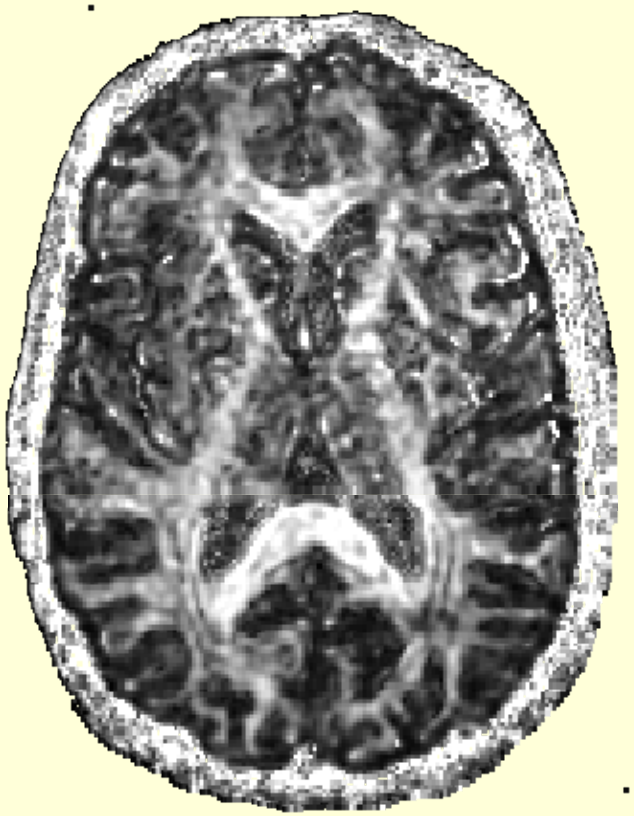




Reduced Anisotropic Diffusion in Older Adults

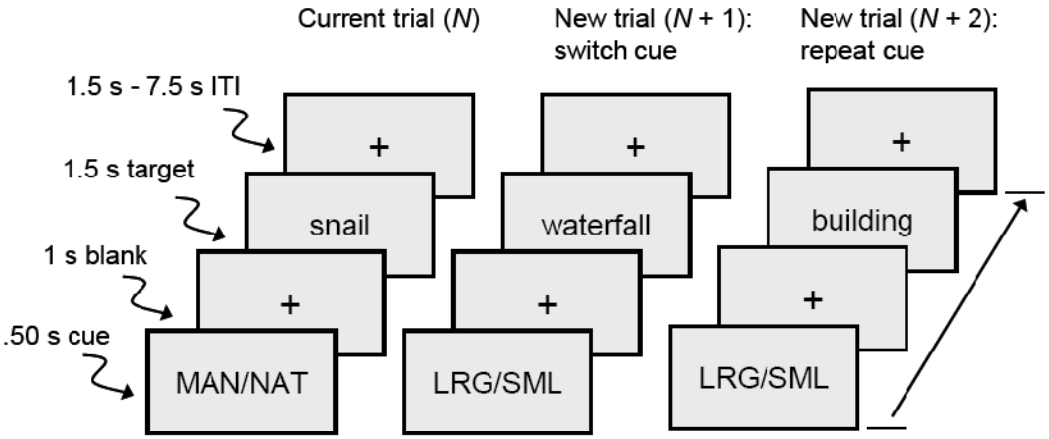
Younger





Older

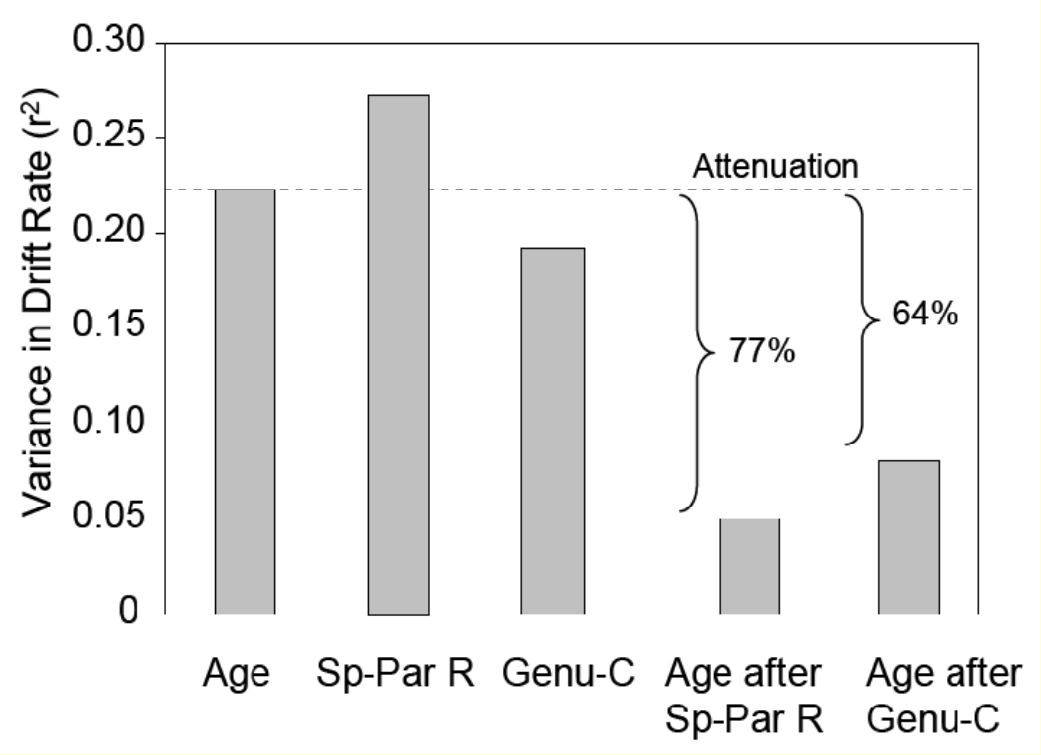
Data from Madden et al. (2007)



Older (60-85y) and younger (18-27y) adults made categorical judgments.

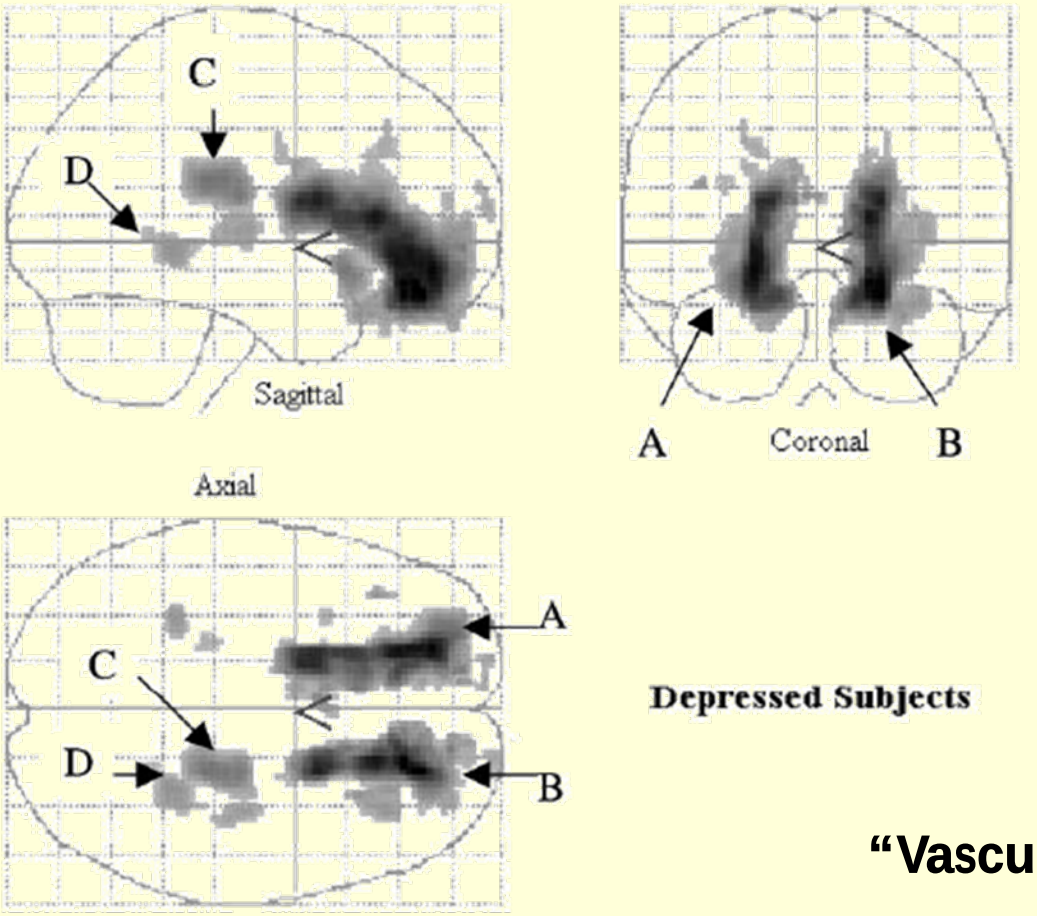
We modeled information accumulation (i.e., drift rate) using a model for each subject's response time.

Age-related variance in information accumulation was reduced dramatically, when integrity of two fiber tracts was included in the model.



Madden et al. (*in press*)

White-Matter Pathology in Aging

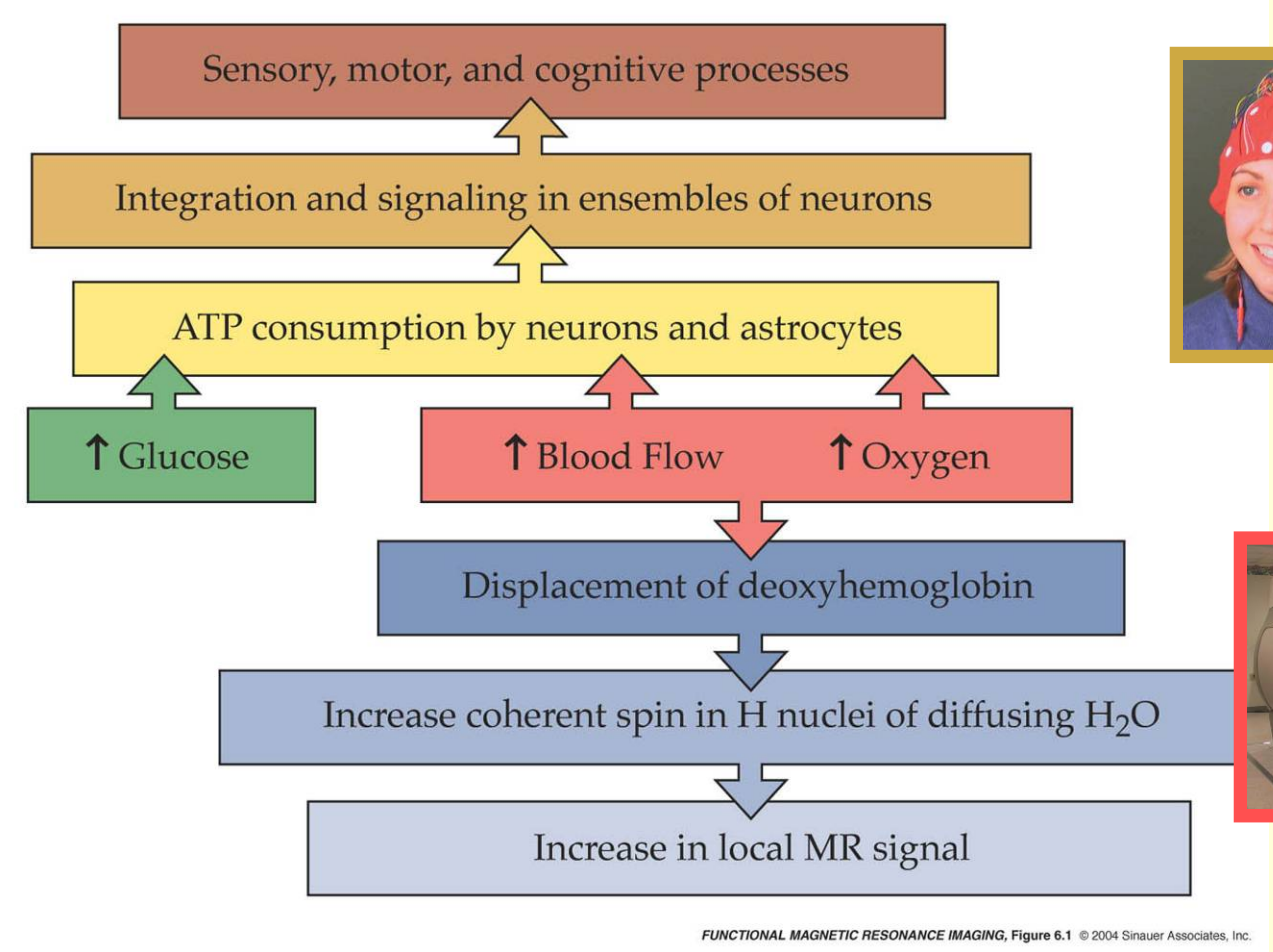


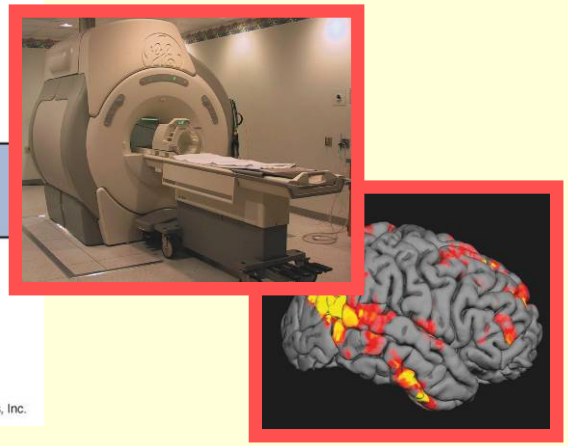
Taylor et al. (*2003*)

"Vascular Depression Hypothesis":

Vascular disease →
white matter hyperintensities →
late-life depression

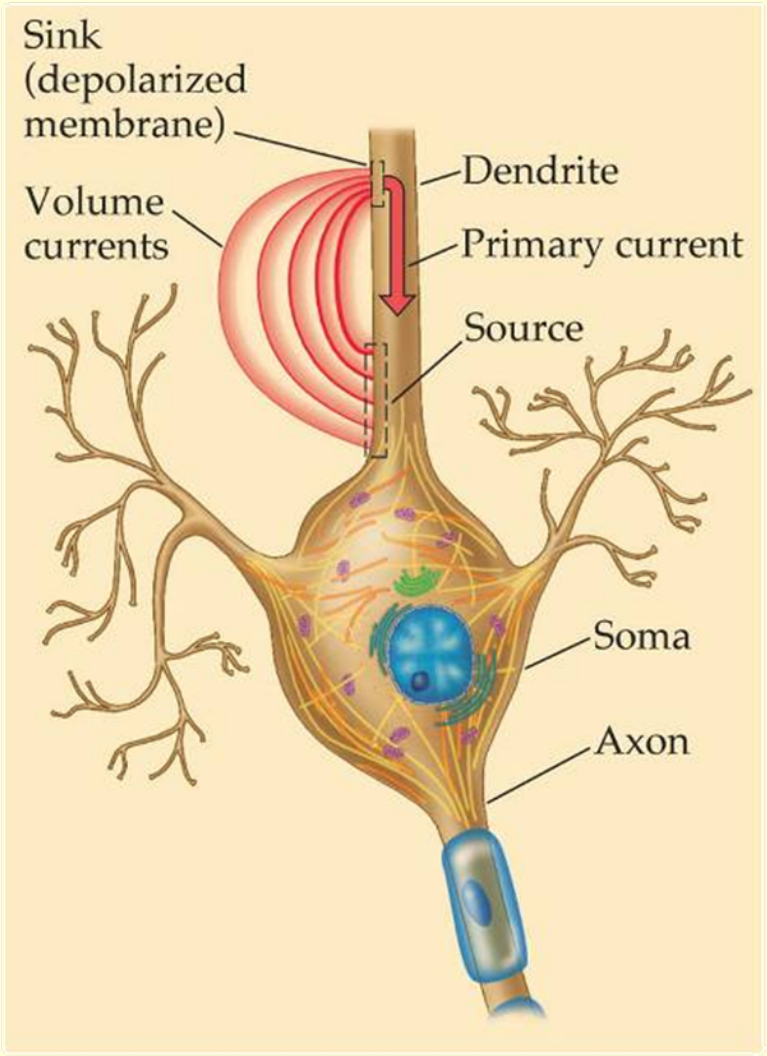
Neuroimaging of *Function*



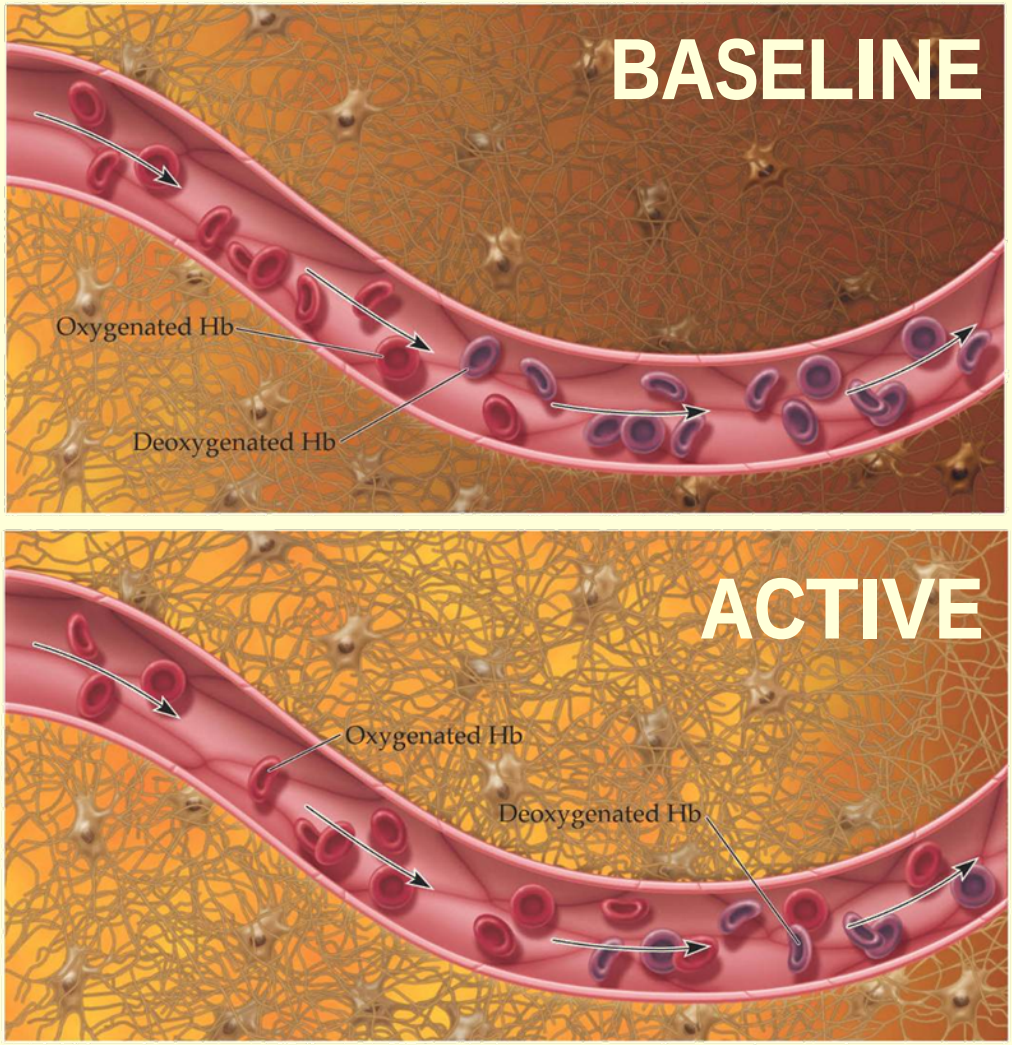


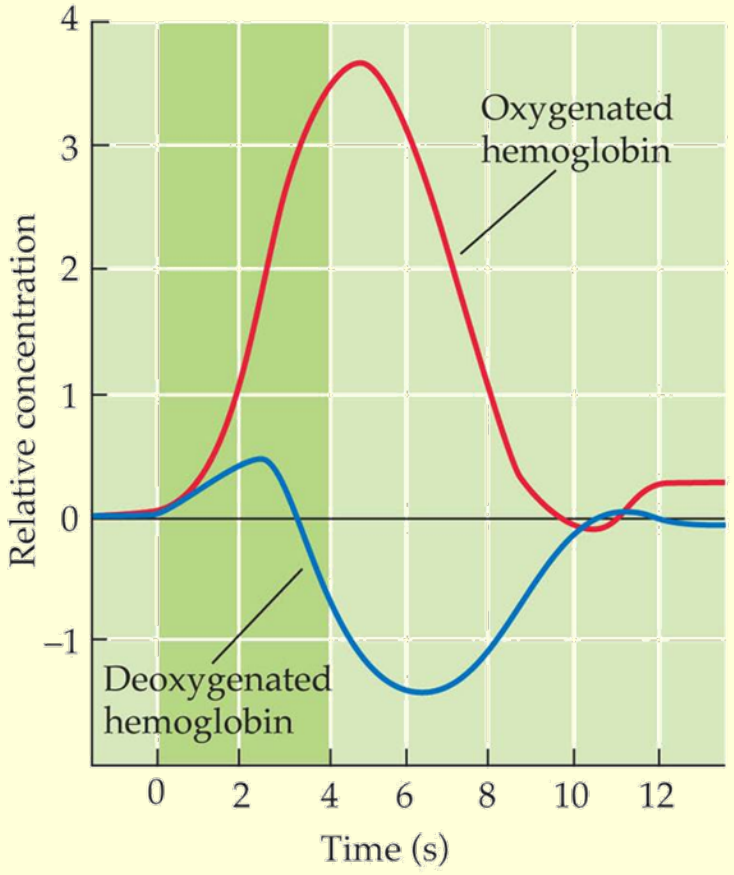
Cardinal challenge: distinguishing cognitive from physiological changes

Neuronal origins of the fMRI Hemodynamic Response



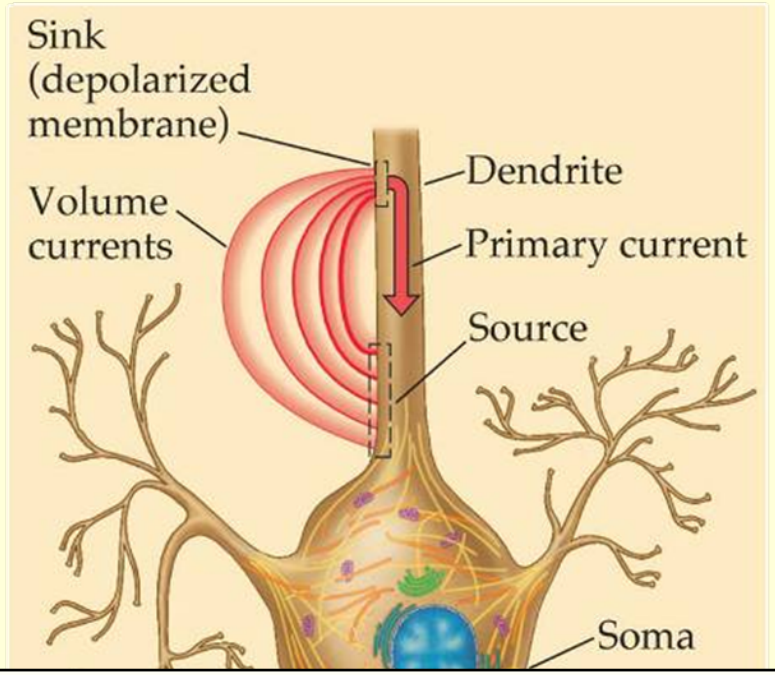
Blood-Oxygenation-Level-Dependent (BOLD) fMRI

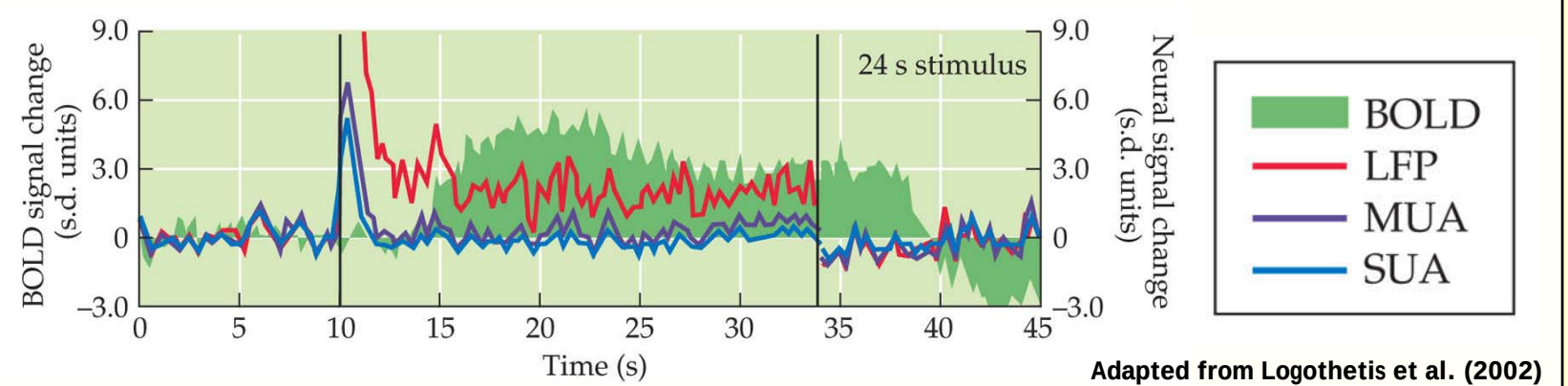




After Malonek & Grinvald (1996)

Neuronal origins of the fMRI Hemodynamic Response

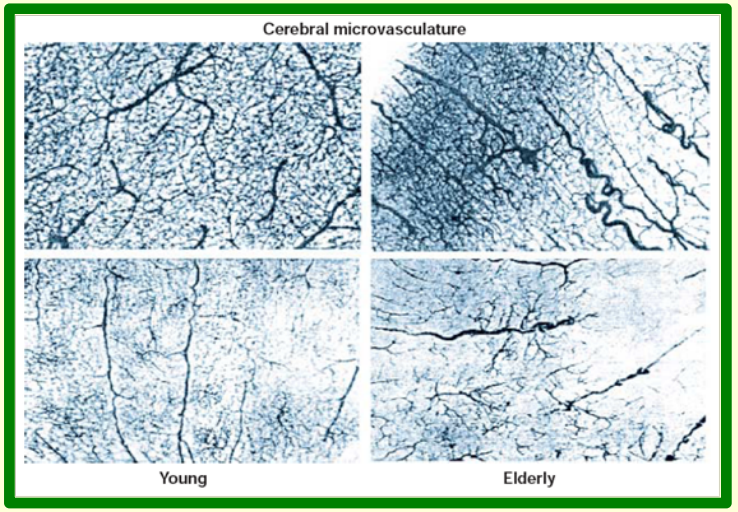




Adapted from Logothetis et al. (2002)

Age-Related Changes in Cerebrovascular System

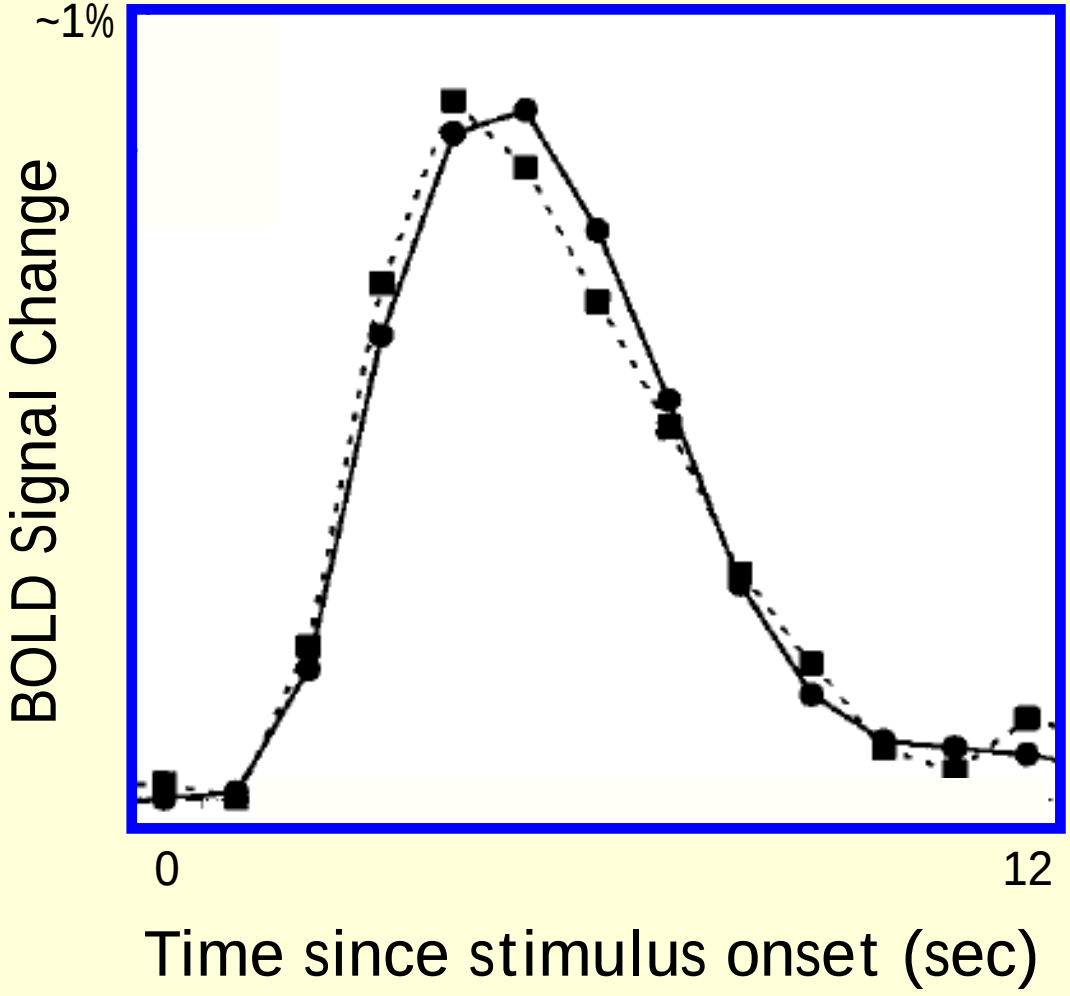
- Thickening of vessel walls
- Hypertension
- Venous occlusions
- Changes in capillary structure
- Reduced blood flow
- Reduced oxygen consumption ($CMRO_2$)



Fang (1976)

Structural and physiological changes associated with normal aging may have consequences for neuroimaging methods.

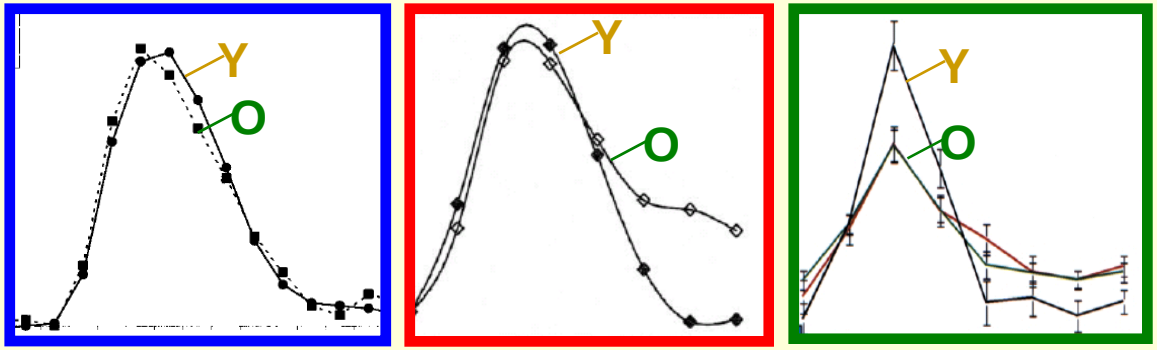
Do Cerebrovascular Changes Influence BOLD Signal?



Huettel et al. *(2001)*

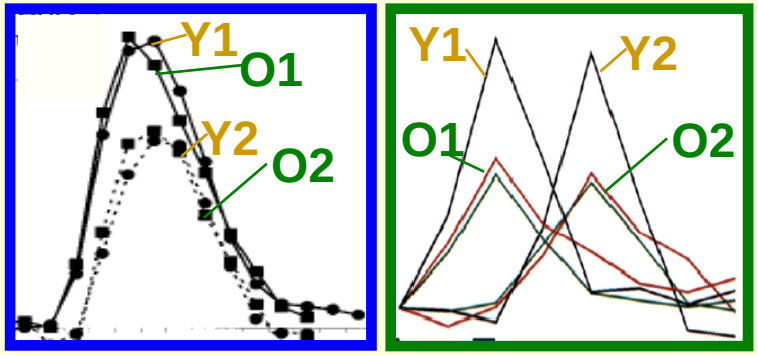
BOLD Amplitude

Generally similar or slightly reduced in older (O) compared to younger (Y) adults.



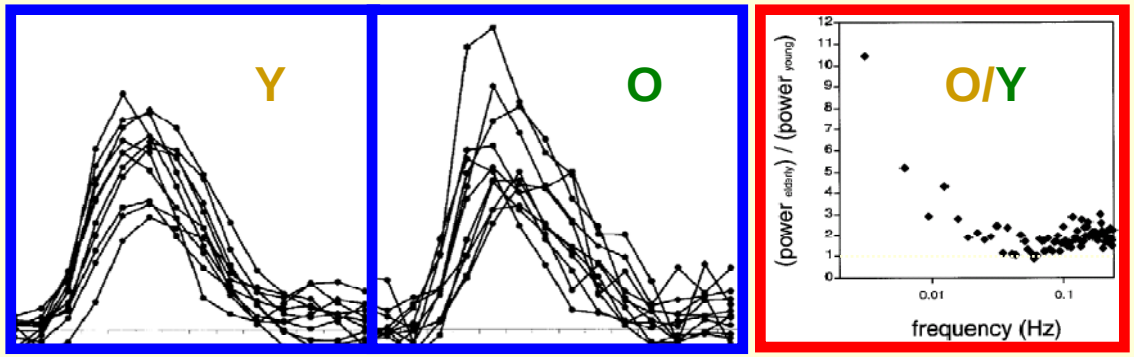
BOLD Refractory Effects

Similar refractory properties (i.e., to multiple events in rapid succession) in younger and older adults.

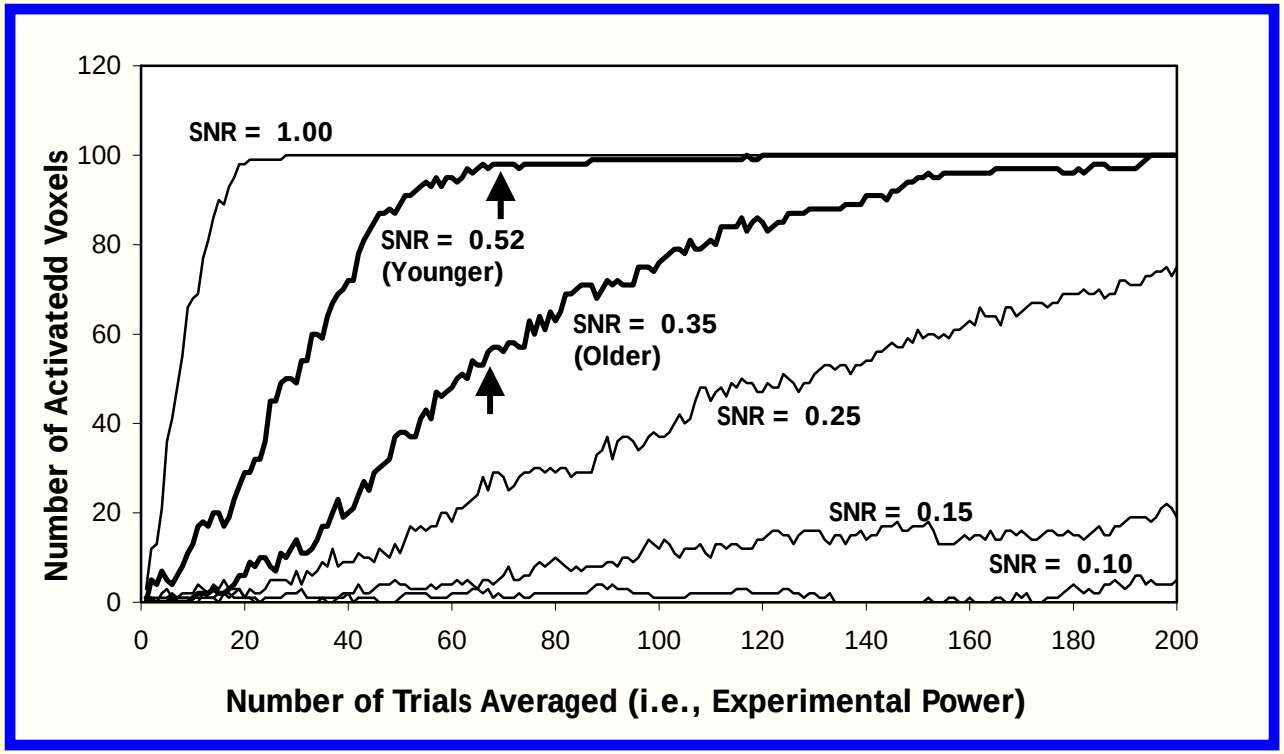


BOLD Signal-Noise Ratio

Reduced signal-noise ratio (SNR) in older adults.



D'Esposito et al. *(1999)*
Buckner et al. *(2000)*
Huettel et al. *(2001)*

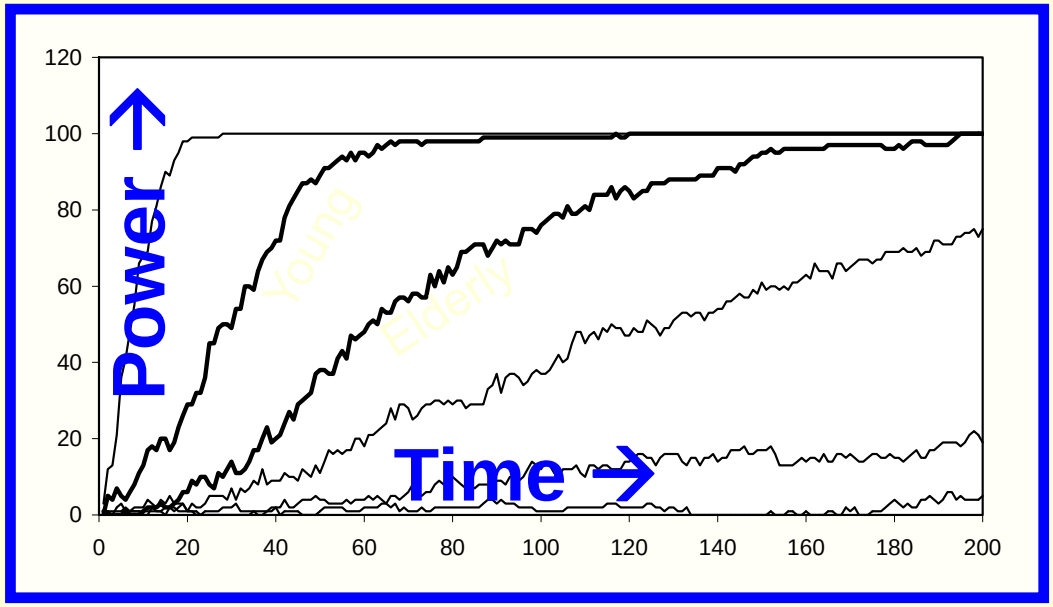


Huettel et al.
(2001)

Age-related differences in how much of the brain is activated may reflect differences in age-related noise, not cognition.

Aging and BOLD fMRI: Practical Issues

- Reduced tolerance for time in scanner



Aging and BOLD fMRI: Practical Issues

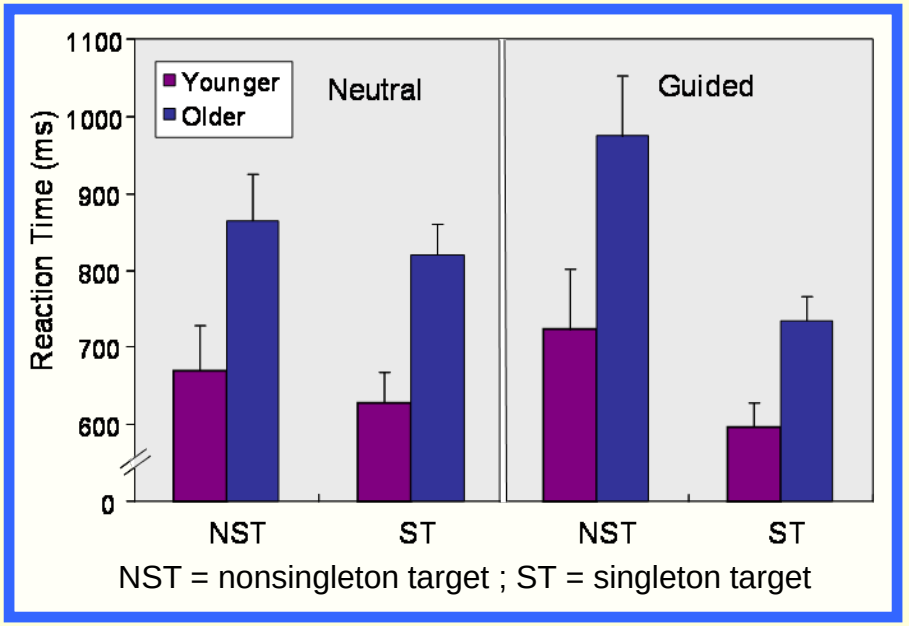
- Reduced tolerance for time in scanner
- Reduced sensory abilities

Aging and BOLD fMRI: Practical Issues

- Reduced tolerance for time in scanner
- Reduced sensory abilities
- Reduced performance on many tasks

Age group	Task condition		
	Standards	Novels	Targets
Younger adults	339 (45)	440 (73)	461 (67)
Older adults	384 (62)	518 (78)	509 (75)

Digit-symbol RT (in ms)			
Younger		Older	
1,331.00	(183.00)	1,713.00	(250.00)



Excerpts from Madden et al. (2004a, 2004b, 2006)

Aging and BOLD fMRI: Practical Issues

- Reduced tolerance for time in scanner
- Reduced sensory abilities
- Reduced performance on many tasks
- Biased sample selection

Younger adults and older adults did not differ significantly with regard to the number of years of education (younger adults' M = 16.7 years; older adults' M = 17.5 years).

all participants reported being free of significant health problems such as atherosclerotic cardiovascular disease or hypertension. None of the participants reported taking medications known to affect cognitive functioning or cerebral blood flow.

Is the typical older adult someone who

is college-educated++,

has no significant health problems,

is taking only minimal medication,

and has a vocabulary (etc.) similar to a Duke undergraduate?

Table 1
Participant Characteristics by Age Group

	Younger		Older	
Variable	*M*	(*SD*)	*M*	(*SD*)
Age (in years)	22.80	(1.91)	67.45	(5.87)
MMSE	29.75	(0.44)	28.90	(1.12)
Education (in years)	16.15	(1.46)	17.20	(1.44)
Vocabulary	65.35	(3.56)	66.10	(3.02)
Acuity	16.50	(3.66)	22.75	(8.35)
Color vision	14.00	(0.00)	13.75	(0.64)
Digit-symbol RT (in ms)	1,331.00	(183.00)	1,713.00	(250.00)
Digit-symbol accuracy (%)	98.00	(1.84)	97.71	(2.31)

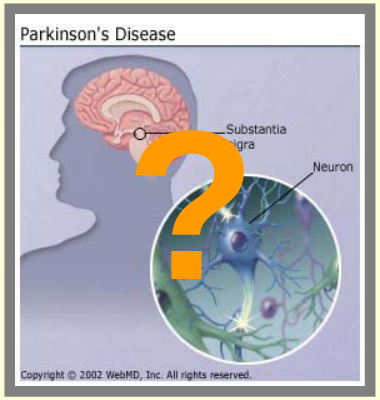
Excerpts from Madden et al. (2004a, 2004b)

Aging and BOLD fMRI: Practical Issues

- Reduced tolerance for time in scanner
- Reduced sensory abilities
- Reduced performance on many tasks
- Biased sample selection
- Different motivation for participating

> Although important objections have been raised to the way financial incentives are often structured (e.g., Harrison 1989; 1992), experimental economists who do not use them at all can count on not getting their results published. Camerer and Hogarth (1999) reported that "a search of the *American Economic Review* from 1970–1997 did not turn up a single published experimental study in which subjects were not paid according to performance" (p. 31).

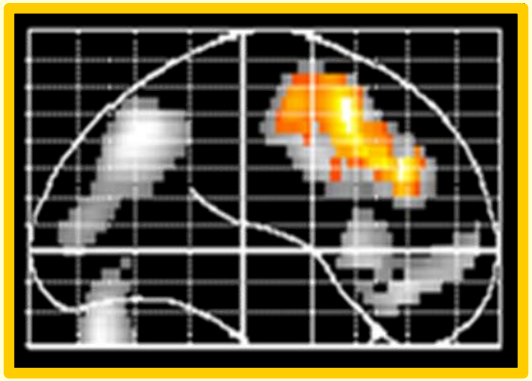
Excerpt from Hertwig & Ortmann (2001)

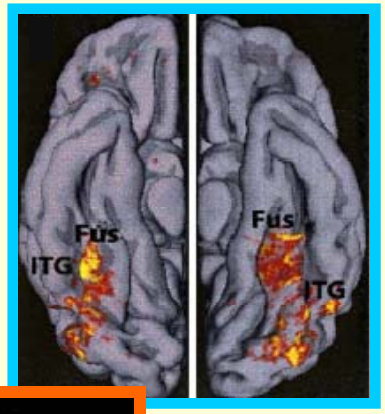


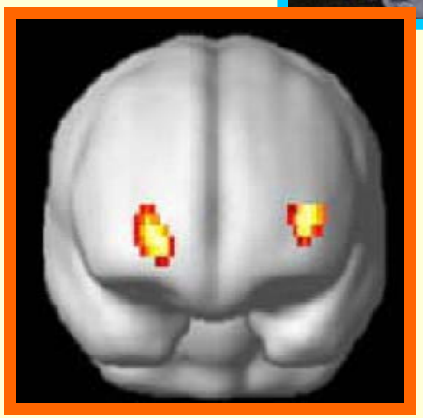
Insights from Cognitive Neuroscience

Guideline #1: Avoid Direct Comparisons

Guideline #2: Seek *Neural Constructs*



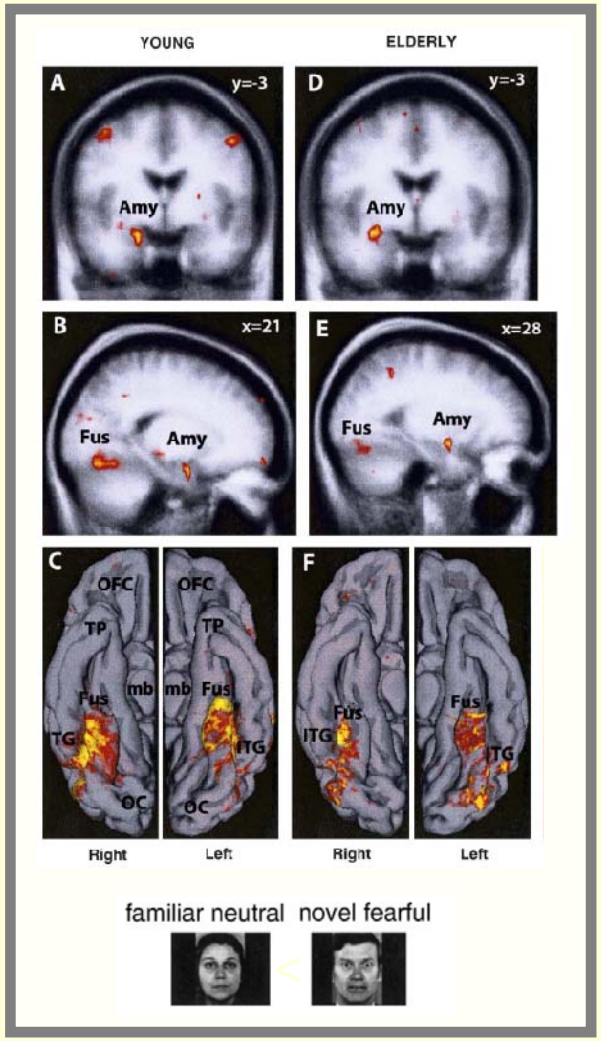




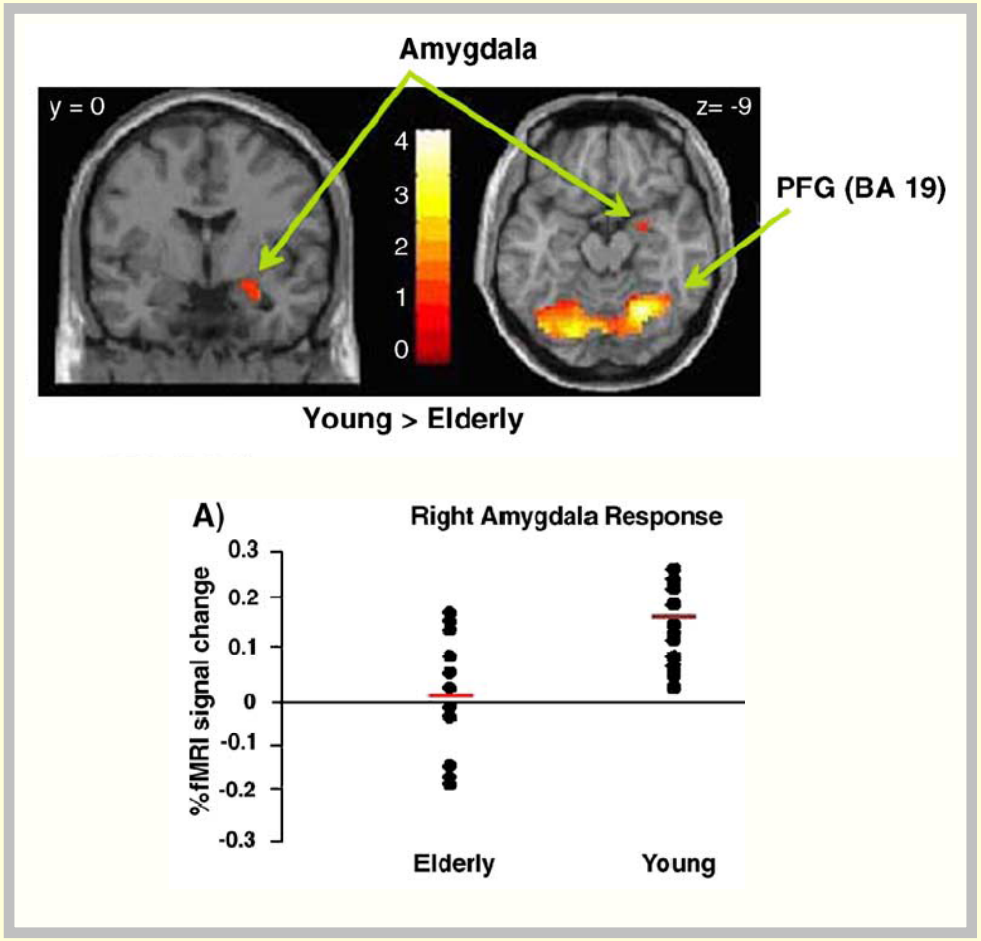
	Younger Adults	Older Adults
Non-selective decrease		
Selective decrease		
Selective decrease and selective increase		

Adapted from Gazzaley & D'Esposito (2004)

Examples of Non-Selective Decreases



Wright et al., 2006



Tessitore et al., 2005

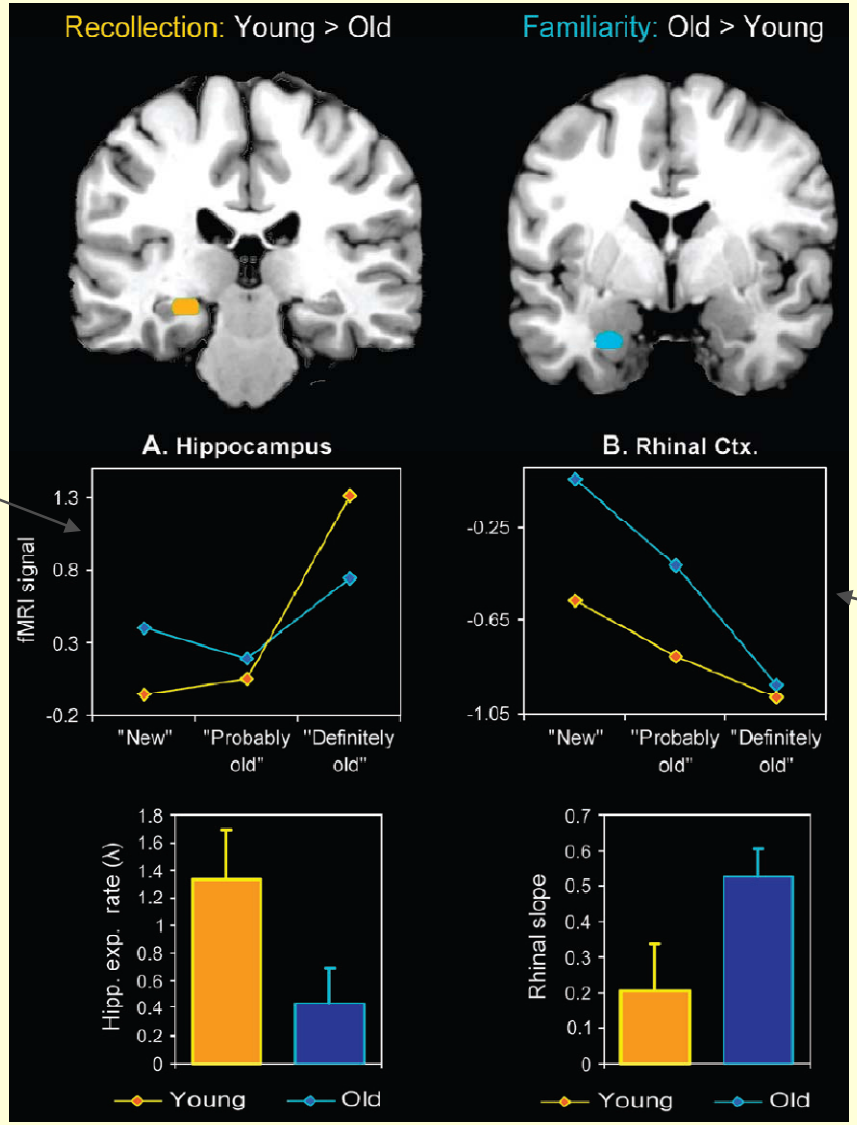
Do not simply compare younger and older adults on some neuroimaging measure.

Compare

- **age * condition interactions,**
- **parametric effects within specific groups,**
- **or analyses that predict BOLD signal based on age and psychometric data**

Age * Condition interactions

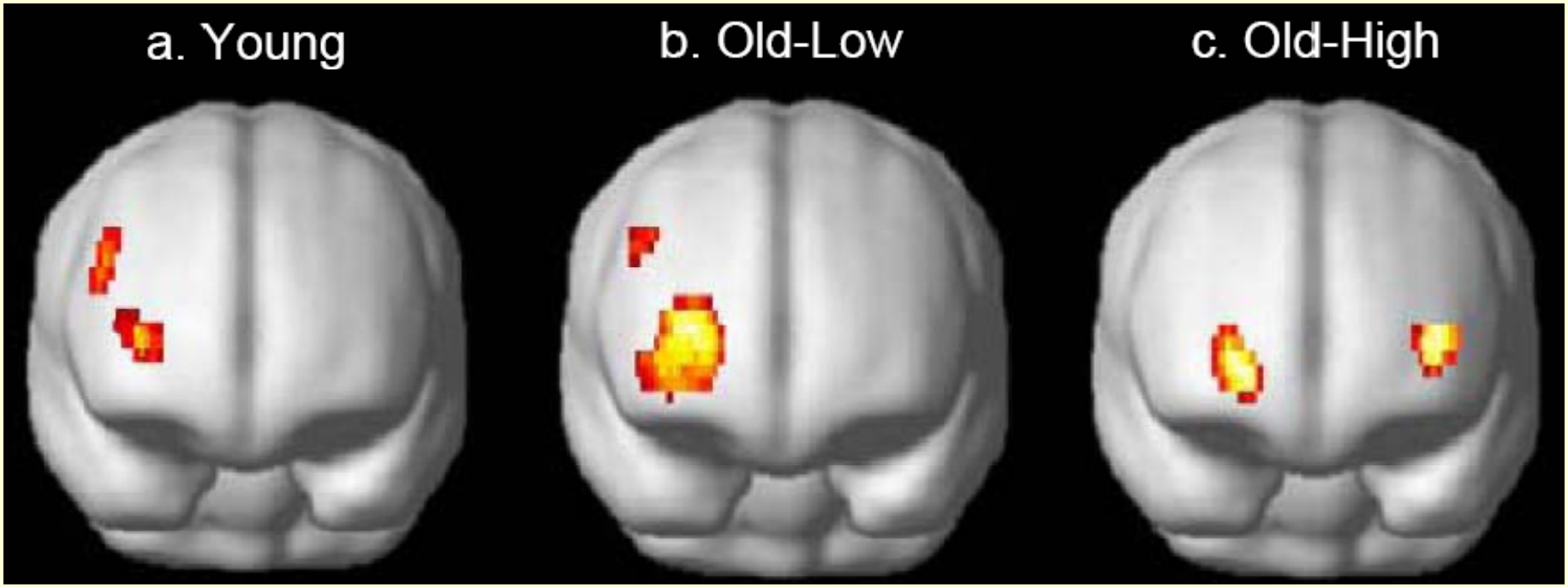
Older Adults: Attenuation of recollection-based activation in hippocampus.



Older Adults: Enhancement of familiarity-based activation in rhinal cortex.

Cabeza et al., 2006

Neural Construct: *Functional Compensation*

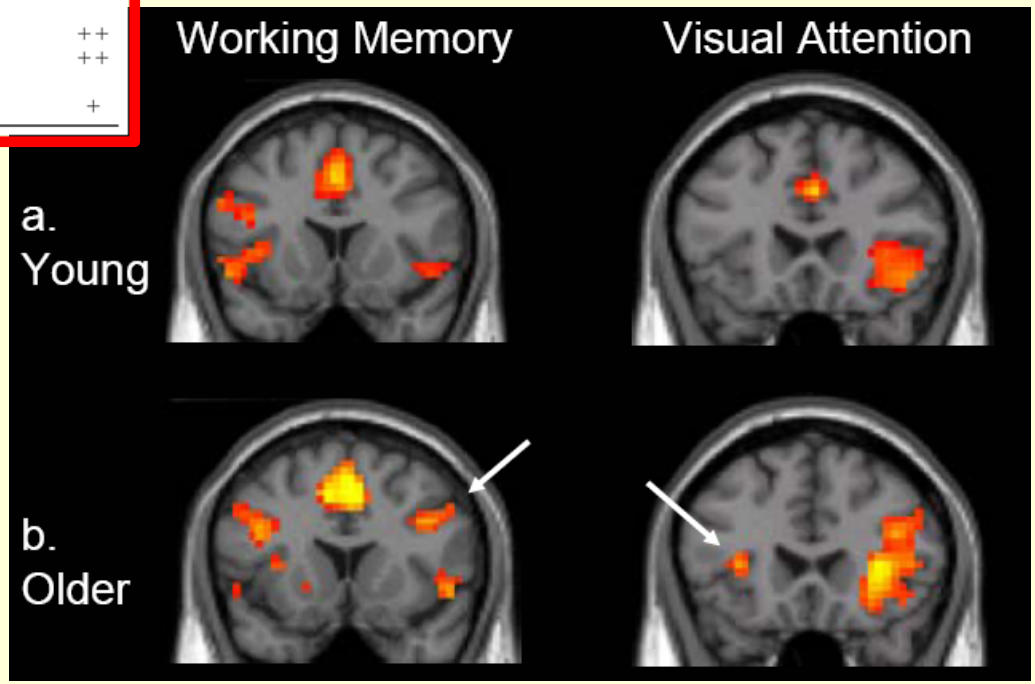


Cabeza et al., 2002a

In a memory retrieval task, Older adults who perform similarly to younger adults (Old-High) show increased activation in left PFC, compared to older adults with impaired performance.

Broadening a Neural Construct …

Imaging technique and materials or task	Younger		Older	
	Left	Right	Left	Right
Episodic Retrieval				
PET: Word-pair cued-recall (Cabeza, Grady, et al., 1997)	−	++	+	+
PET: Word-stem cued-recall (Bäckman et al., 1997)	−	+	+	+
PET: Word recognition (Madden, Gottlob, et al., 1999)	−	+	++	++
PET: Face recognition (Grady et al., 2002)	−	++	+	+
Episodic Encoding/Semantic Retrieval				
fMRI: Word-incidental (Stebbins et al., 2002)	++	+	+	+
fMRI: Word-intentional (Logan & Buckner, 2001)	++	+	+	+
fMRI: Word-incidental (Logan & Buckner, 2001)	++	+	++	++
Working Memory				
PET: Letter DR (Reuter-Lorenz et al., 2000)	+	−	+	+
PET: Location DR (Reuter-Lorenz et al., 2000)	−	+	+	+
PET: Number N-back: (Dixit et al., 2000)	+	+++	++	++
Perception				
PET: Face matching (Grady et al., 1994, Exp. 2)	−	+	++	++
PET: Face matching (Grady et al., 2000)	+	+++	++	++
Inhibitory Control				
fMRI: No-go trials (Nielson et al., 2002)	−	+	+	+



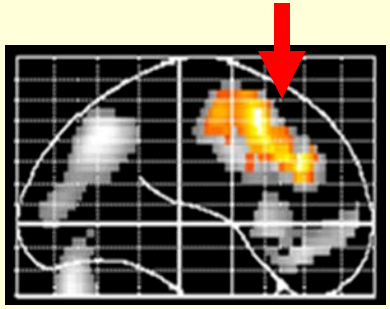
Cabeza, 2002; Cabeza et al., 2004

Divided Attention

F	S	W
H	M	D
B	T	G

vs.

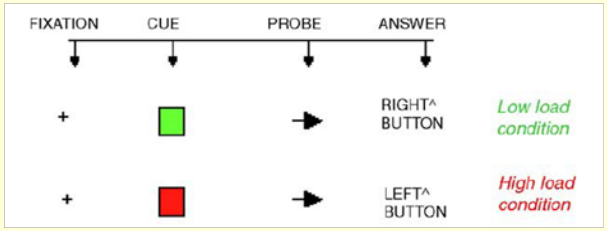
F	S	W
H	M	D
B	T	G

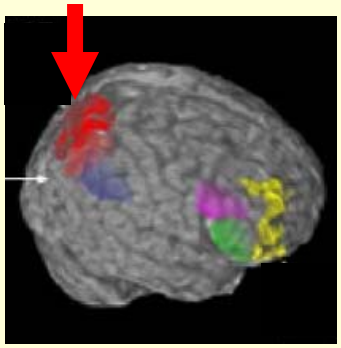


Medial Prefrontal Cortex

Madden et al., 1997

S-R incompatibility

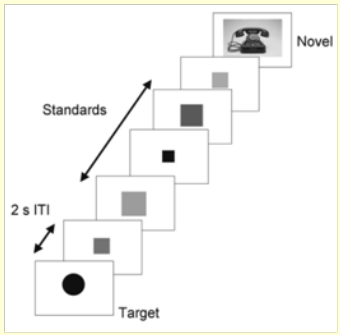


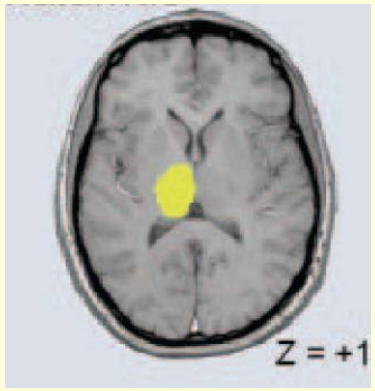


Posterior Parietal Cortex

Rosano et al., 2005

Target Detection

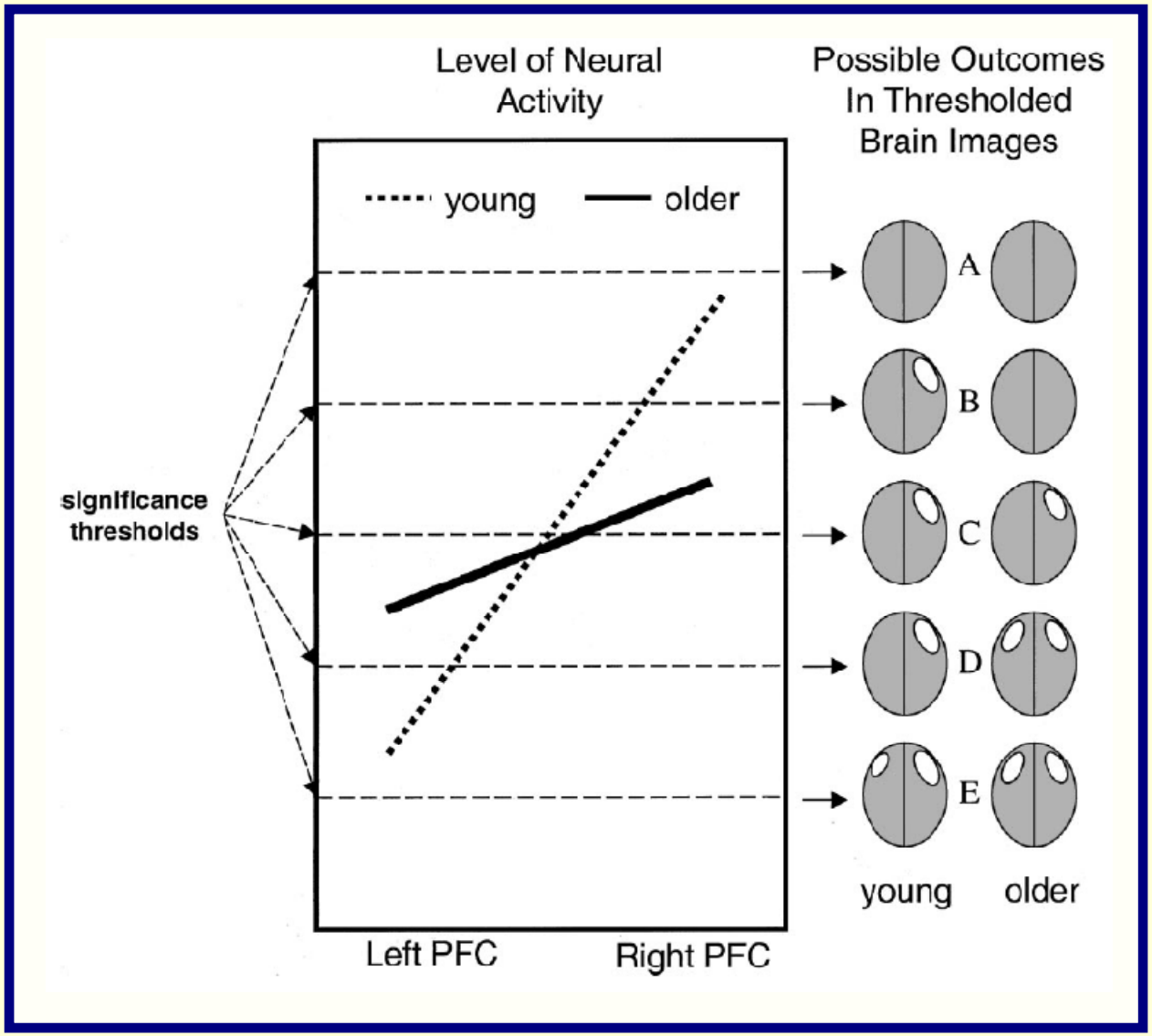




Thalamus / Basal Ganglia

Madden et al., 2004

Compensation: Methodological Caveats

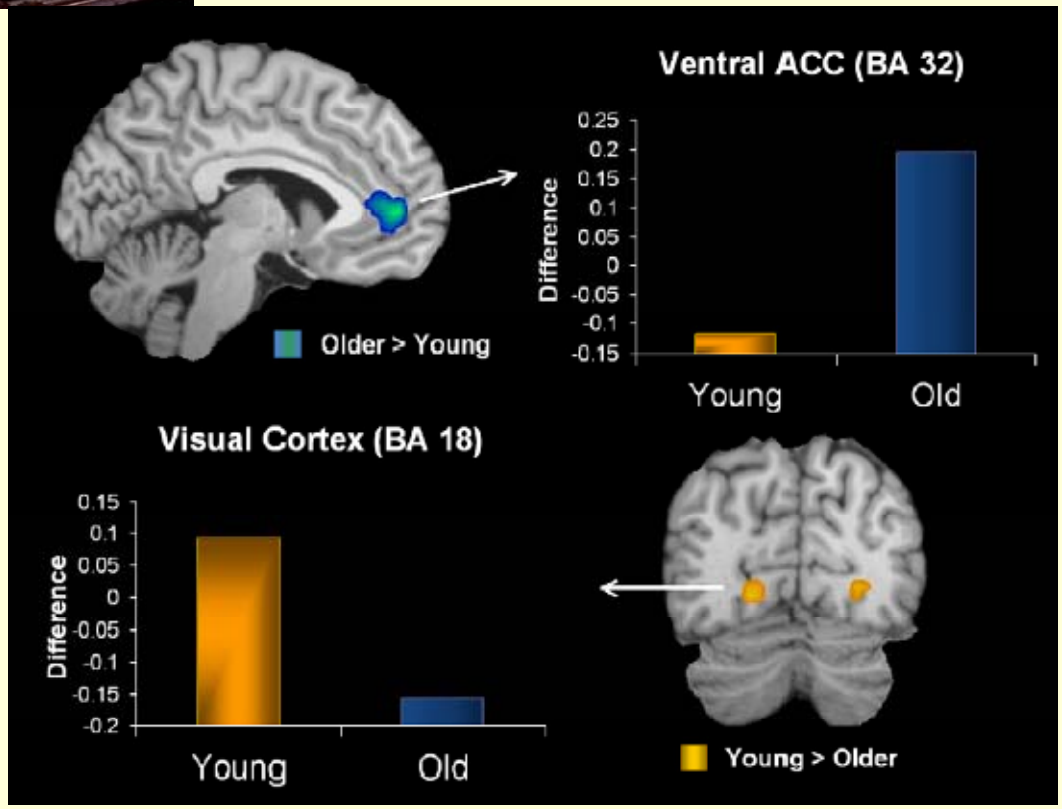


Cabeza, 2002

Neural Construct: *Functional Connectivity*

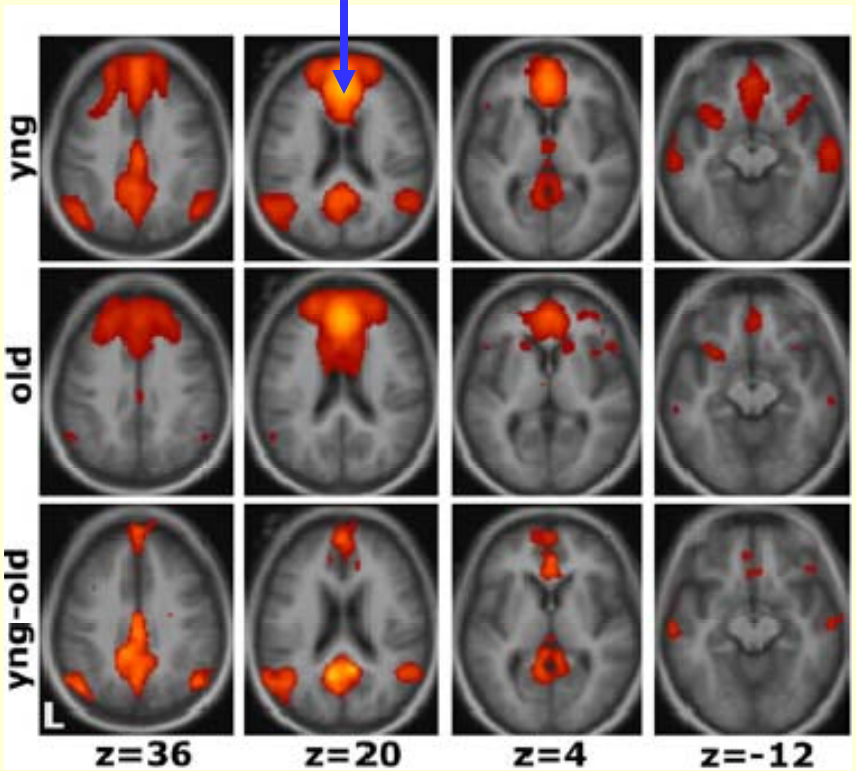
Viewing emotional images leads to activation in a variety of regions (e.g., amygdala).

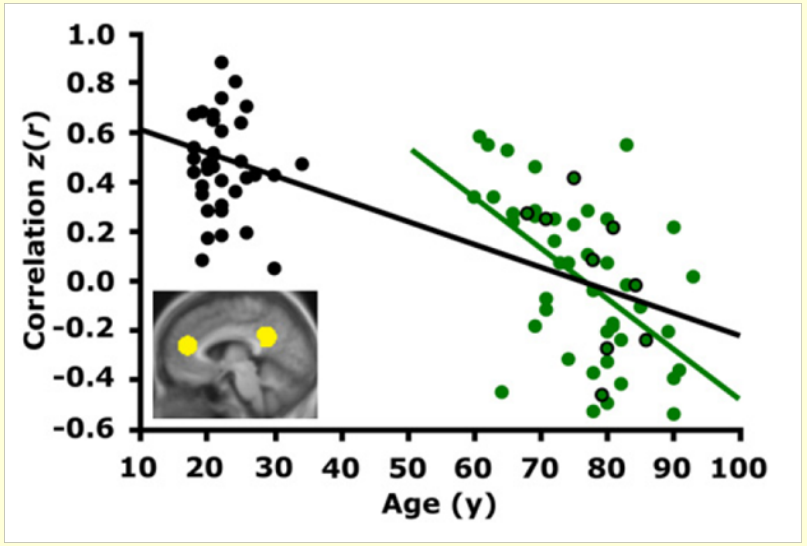
There are age-related changes in the *functional connectivity* between the amygdala and other regions.



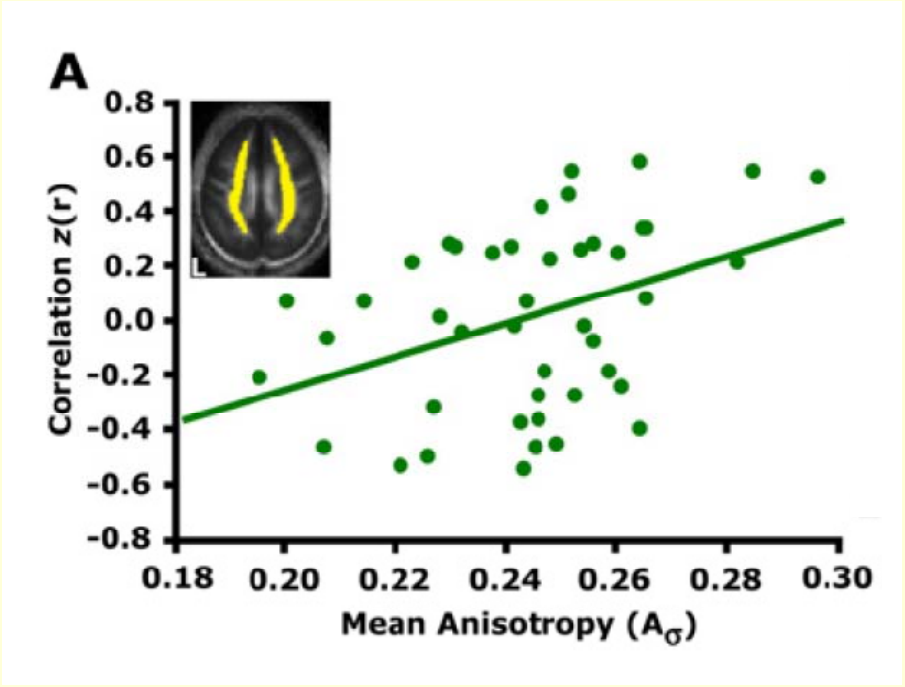
St. Jacques et al. (*in press*)

Changes in functional connectivity persist even in the absence of tasks (i.e., in *default mode* processing)!



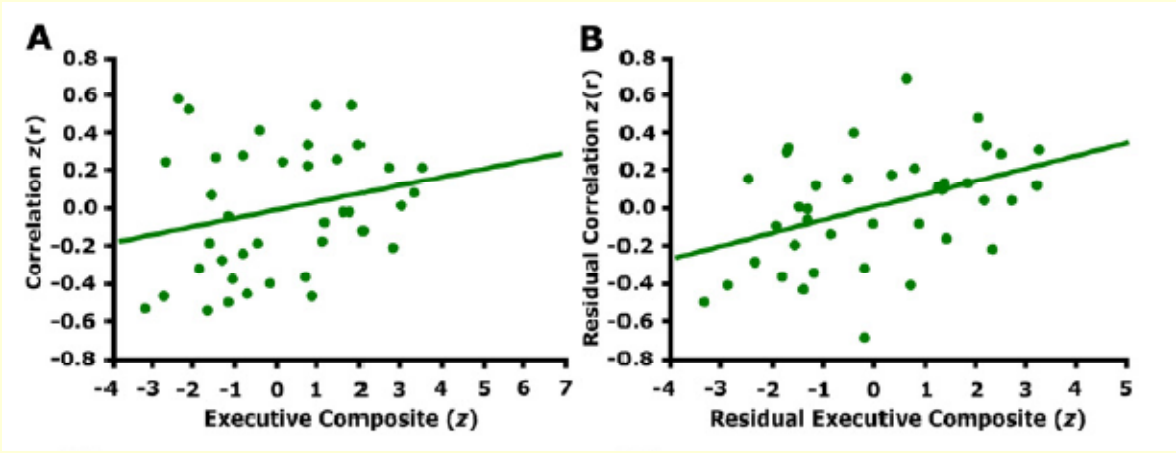


Andrews-Hanna et al., 2007



Functional connectivity is predicted by integrity of white matter pathways...

... and it in turn predicts cognitive performance, including executive function.



When neuroimaging the aging mind, it is rarely sufficient to identify simple age-related effects upon brain function.

Instead, researchers should strive to identify *neural constructs*, or functional patterns that themselves predict age-related differences in behavior.

Caveats and Challenges

- Know your subjects (and their characteristics)
- Neuroimaging is easy… task design is hard…
- Attend to subjects' motivation (& cognition)
- Focus on function, then how it changes w/age
- There are big problems… Ask big questions!

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