Cognitive Neuroscience of Aging:
Linking Cognitive and Brain Aging

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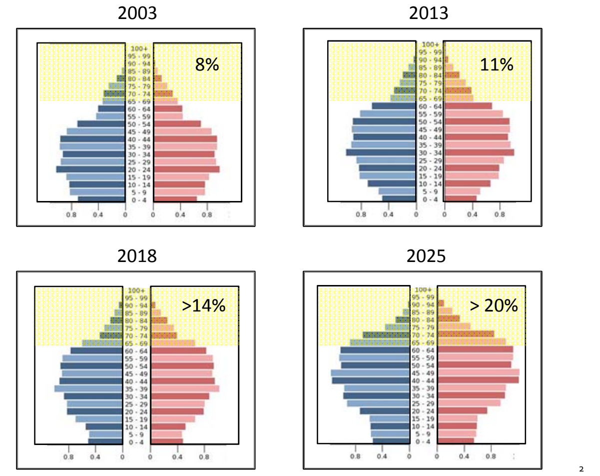
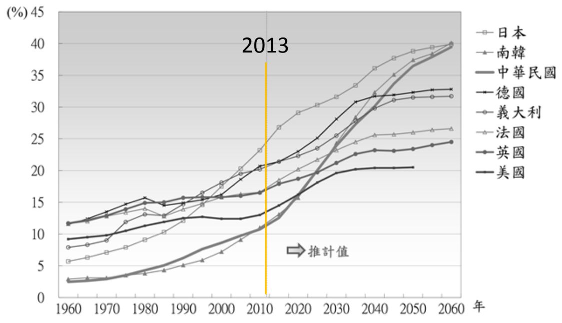


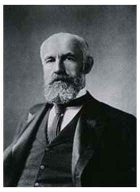
Global aging:
Growing proportion of persons > 65 years



The age wave

Human aging

Brief history

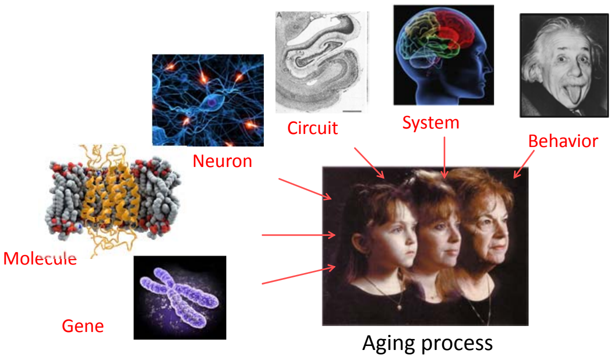


- Granville Stanley Hall (1844-1924) published the book "Senescence,“ a book on aging in 1922 (at age 79)
- By 1946, NIH established a research unit
  - ✓ National Institution on Aging (NIA)
  - ✓ 1958: The Baltimore Longitudinal Study of Aging (BLSA)
- By 1990s, several life-span studies proposed:
  - ✓ 1990: Rotterdam study
  - ✓ 1990: Berlin Aging study (Berliner Altersstudie, BASE)
  - ✓ 1992: The Australian Longitudinal Study of Ageing (ALSA)
  - ✓ 2007: Singapore Longitudinal Aging Brain Study (S-LABS)

The study of human aging:

- Gerontology (“study of old man“ in Greek)
  - ✓ Scientific study of the aging process itself (e.g., physical, mental, and social changes) and special problems of the aged.
- Geriatrics (“old-man healer“ in Greek)
  - ✓ Area of specialization within the filed of medicine that deals with the study of the diseases and care of aged persons
- Neuroscience of aging
  - ✓ Scientific study of the relationship between neural changes and cognitive functions in the elderly

Level of analysis in neuroscience of aging



Circuit

System

Behavior

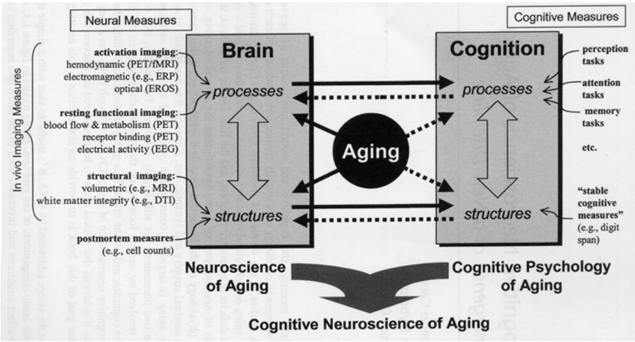
Neuron

Molecule

Gene

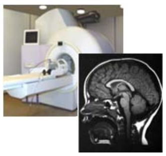
Aging process

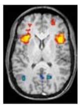
Cognitive Neuroscience of Aging
Cabeza, Nyberg, & Park, 2005



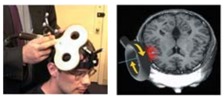
Integration of data from different domains

Neural measures


Structural MRI


Functional MRI


Diffusion MRI


TMS

Cognitive measures

Behavioral responses
(RTs, accuracy)

Neuropsychological
assessment

Methodological considerations:
Participants

- Screening participants (for research on normal aging):
  - ✓ Separate the effects of aging from other factors
  - ✓ Collect demographic and relevant info about the participants:
    - General info: age, sex, education, marital status etc.
    - Medical history (e.g., smoking, alcohol, prescription drug etc.)
    - Hearing and/or vision
    - General cognitive abilities and dementia
      - -- Neuropsychological assessment (e.g., WAIS-R)
      - -- Mini-mental status exam (MMSE) or Montreal Cognitive Assessment (MoCA)
    - Depression and life style
    - Others: handedness, native language, fitness, diet etc.

Methodological considerations:
Participants

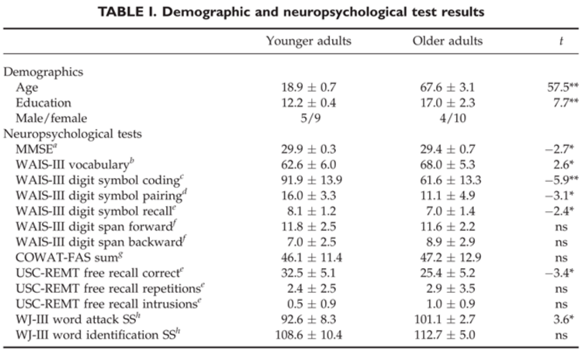
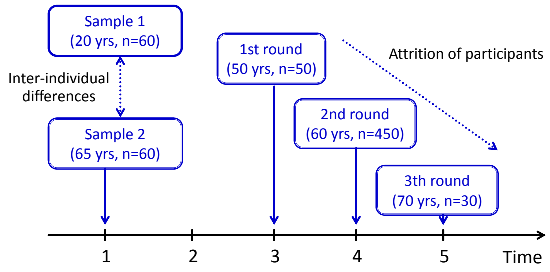


TABLE I. Demographic and neuropsychological test results

	Younger adults	Older adults	*t*
Demographics			
Age	18.9 ± 0.7	67.6 ± 3.1	57.5**
Education	12.2 ± 0.4	17.0 ± 2.3	7.7**
Male/female	5/9	4/10	
Neuropsychological tests			
MMSE[a]	29.9 ± 0.3	29.4 ± 0.7	−2.7*
WAIS-III vocabulary[b]	62.6 ± 6.0	68.0 ± 5.3	2.6*
WAIS-III digit symbol coding[c]	91.9 ± 13.9	61.6 ± 13.3	−5.9**
WAIS-III digit symbol pairing[d]	16.0 ± 3.3	11.1 ± 4.9	−3.1*
WAIS-III digit symbol recall[e]	8.1 ± 1.2	7.0 ± 1.4	−2.4*
WAIS-III digit span forward[f]	11.8 ± 2.5	11.6 ± 2.2	ns
WAIS-III digit span backward[f]	7.0 ± 2.5	8.9 ± 2.9	ns
COWAT-FAS sum[g]	46.1 ± 11.4	47.2 ± 12.9	ns
USC-REMT free recall correct[e]	32.5 ± 5.1	25.4 ± 5.2	−3.4*
USC-REMT free recall repetitions[e]	2.4 ± 2.5	2.9 ± 3.5	ns
USC-REMT free recall intrusions[e]	0.5 ± 0.9	1.0 ± 0.9	ns
WJ-III word attack SS[h]	92.6 ± 8.3	101.1 ± 2.7	3.6*
WJ-III word identification SS[h]	108.6 ± 10.4	112.7 ± 5.0	ns

Methodological considerations:
Experimental designs

- Cross-sectional design
  - ✓ All measurement are performed at about the same time
- Longitudinal design
  - ✓ The same individuals are observed over a period of time



Sample 1 (20 yrs, n=60)

Inter-individual differences

Sample 2 (65 yrs, n=60)

1st round (50 yrs, n=50)

2nd round (60 yrs, n=450)

3th round (70 yrs, n=30)

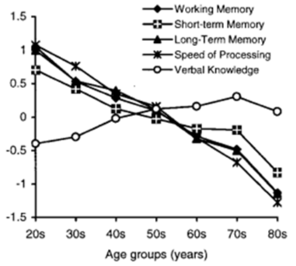
Attrition of participants

Methodological considerations:
Experimental designs

- Cross-sectional design
  - ✓ Age-related differences
  - ✓ Advantages
    - Easier and less costly
    - Mostly descriptive
  - ✓ Disadvantages
    - Cohort effects
- Longitudinal design
  - ✓ Age-related changes
  - ✓ Advantages
    - Intra- individual changes
  - ✓ Disadvantages
    - Drop out (illness etc.)
    - Learning effects
    - research personnel turnover
    - cost in time and money
    - technology advanced

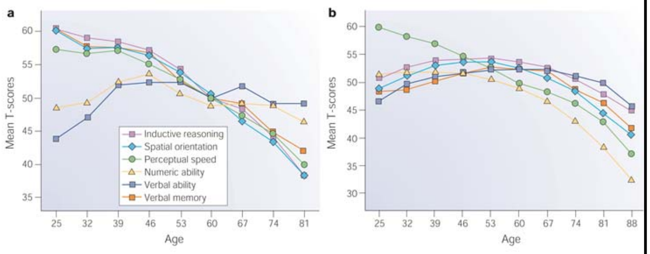
Cognitive aging
Park et al., 2002

- Cross-sectional data: stable verbal-crystallized knowledge and lower fluid abilities are typical in normal aging



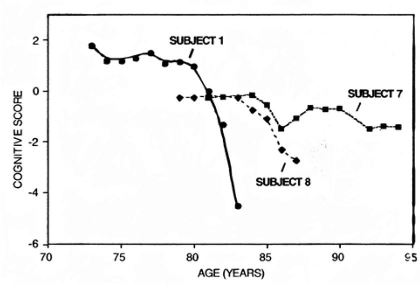
Cognitive aging
Schaie, 1996

- Cross-sectional data
- 7-year longitudinal data



Cognitive aging
Rubin, 1998

- Greater variability across individuals at an old age



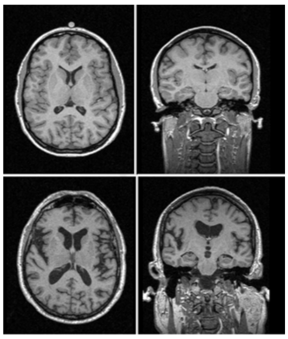
Cognitive aging
Summary

- Cognitive changes in adulthood are multidimensional
  - ✓ Cognitive mechanics tends to decline with aging
    - Includes speed and accuracy of processes
    - Influenced by biology and heredity
    - Reflect the neurophysiological architecture of the brain developed through evolution
  - ✓ Cognitive pragmatics may improve with aging
    - Reading, writing, and educational qualifications
    - Professional skills and language comprehension
    - Knowledge of self and life skills

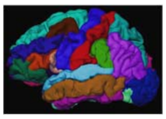
Brain aging:
Structural changes in the elderly brain

Normal young adult
(mid 20's)

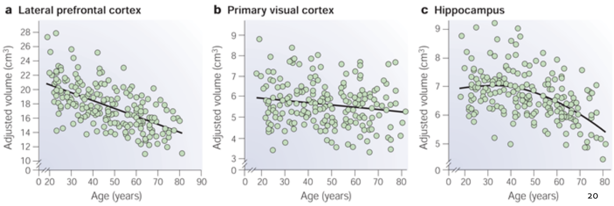
Normal older adult
(late 70's)



Brain aging: gray matter
Raz et al., 2004



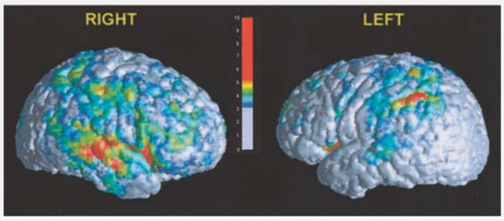
- Cross-sectional MRI volumetric data: different brain regions exhibit different patterns of volumetric shrinkage across the lifespan



Brain aging: gray matter

Resnick et al., 2003

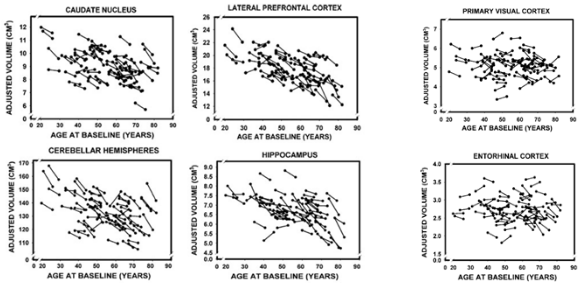
- Longitudinal MRI volumetric data: significant longitudinal tissue loss in specific gray matter regions: most pronounced for orbital and inferior frontal, insular, inferior parietal, and mesial temporal regions



Brain aging: gray matter

Raz et al., 2005

- Reduce with age
- Preserved with age



Brain aging: white matter

- Measurement using diffusion tensor imaging (DTI)
  - ✓ MR diffusion tensor imaging (DTI) is a non-invasive, in vivo method for characterizing the integrity of the microstructure of white matter fibers and cortical connectivity

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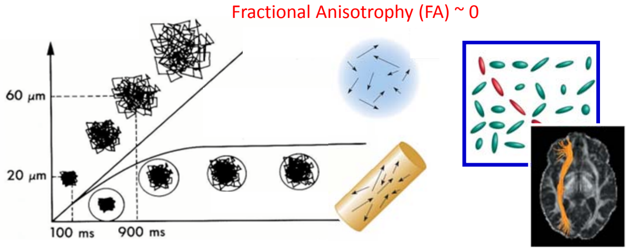
Diffusion tensor imaging (DTI)

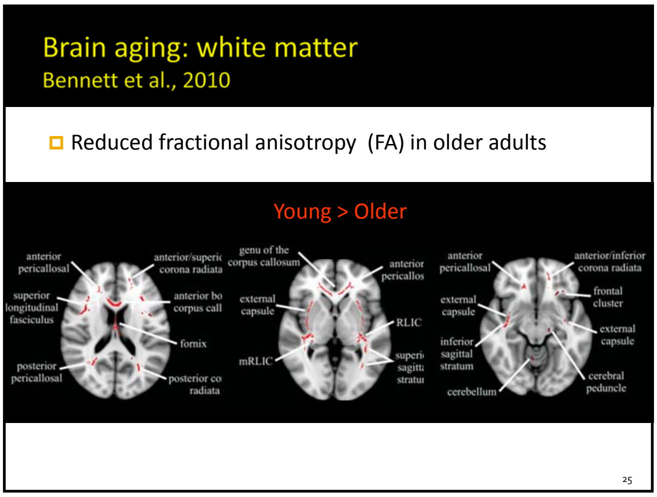


Isotropic diffusion

Fractional Anisotrophy (FA) ~ 0

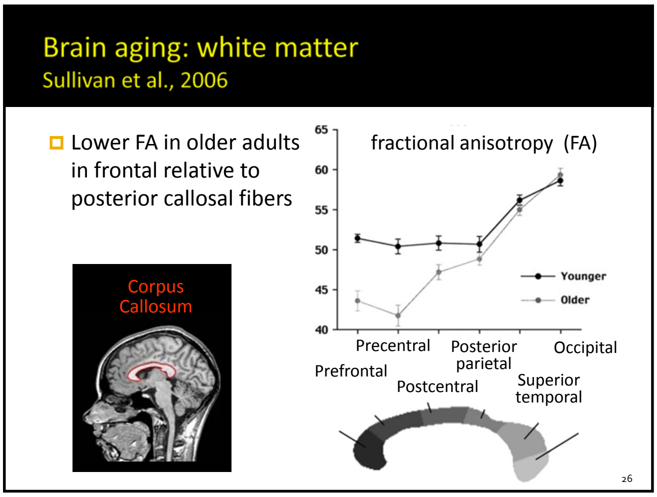
Anisotropic diffusion

Fractional Anisotrophy (FA) ~ 1



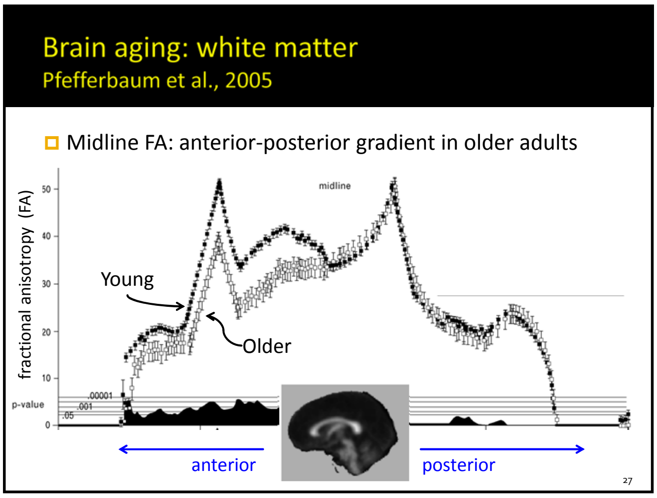
Brain aging: white matter
Bennett et al., 2010

- Reduced fractional anisotropy (FA) in older adults



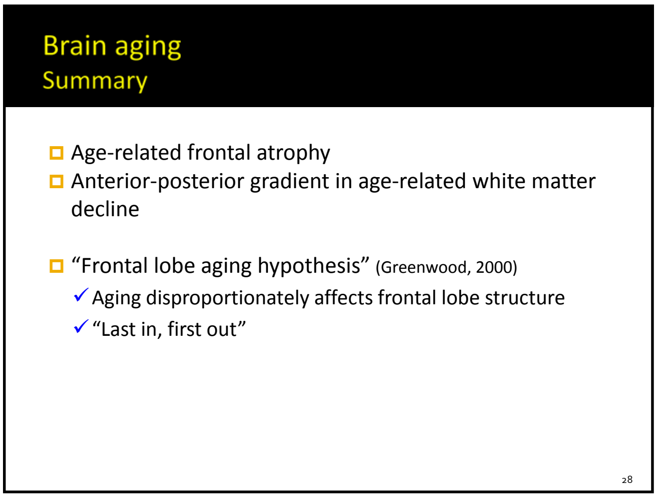
Brain aging: white matter
Sullivan et al., 2006

- Lower FA in older adults in frontal relative to posterior callosal fibers



Brain aging: white matter
Pfefferbaum et al., 2005

- Midline FA: anterior-posterior gradient in older adults



Brain aging
Summary

- Age-related frontal atrophy
- Anterior-posterior gradient in age-related white matter decline

- "Frontal lobe aging hypothesis" (Greenwood, 2000)
  - ✓ Aging disproportionately affects frontal lobe structure
  - ✓ "Last in, first out"

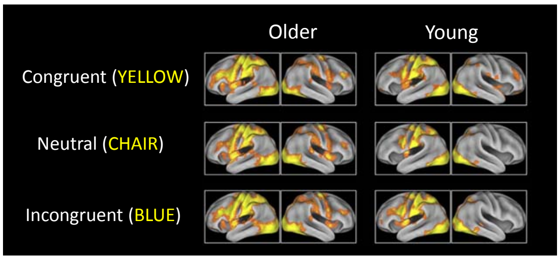
Brain aging
Age-related changes in neural activity

- Age-related frontal over-activation
- Hemispheric Asymmetry Reduction in OLDer adults (HAROLD)
- Posterior-Anterior shift in aging (PASA)

- Reduced distinctiveness of neurocognitive representations

Brain aging
Age-related changes in neural activity

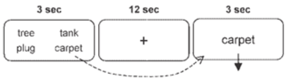
- Age-related frontal over-activation
  - ✓ Increased neural effort involved in cognitive processing
  - ✓ Frequently reported across a variety of cognitive domains



Prakash et al., 2009

Brain aging
Age-related changes in neural activity

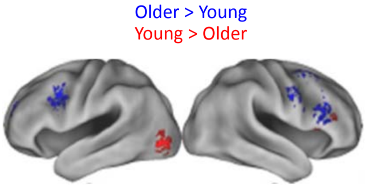
- Hemispheric Asymmetry Reduction in OLDer adults (HAROLD)
  - ✓ Whereas young adults typically engage left-lateralized brain activity (e.g., verbal working memory), older adults show bilateral brain activity.



Cabeza et al., 2004
verbal working memory (fMRI)

Brain aging
Age-related changes in neural activity

- Posterior-Anterior shift in aging (PASA)
  - ✓ Age-related reduction in occipitotemporal activity coupled with age-related increase in frontal activity
  - ✓ Frequently reported across a variety of cognitive domains



Spreng et al., 2010

Brain aging:
Neural mechanisms of age-related frontal over-activation

- Greater frontal activity w/ age is typically interpreted as being compensatory
  - ✓ Aging brain attempts to counteract neural decline by reorganizing its function
  - ✓ Compensate for older adults' optimal behavioral performance

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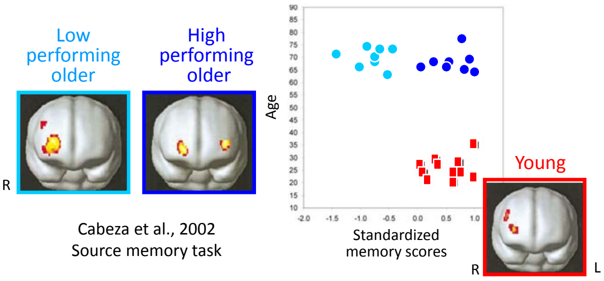
Age-related frontal over-activation compensates for improving performance

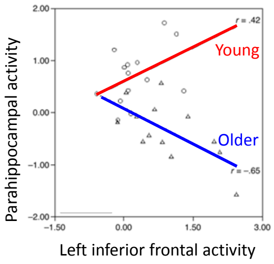
- The greater frontal activity in older adults is associated with better performance

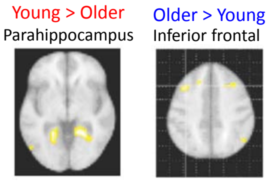


Cabeza et al., 2002
Source memory task

Age-related frontal over-activation compensates for decreased medio-temporal activity

- High levels of inferior prefrontal activation are associated with low levels of parahippocampal activation

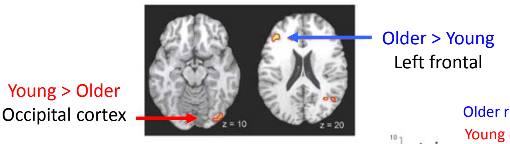


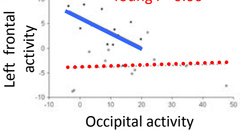


Gutchess et al., 2005
Memory encoding task

Age-related frontal over-activation compensates for reduced ventral visual function

- Age-related increases in prefrontal activity are negatively correlated with decreased occipital activity in older adults

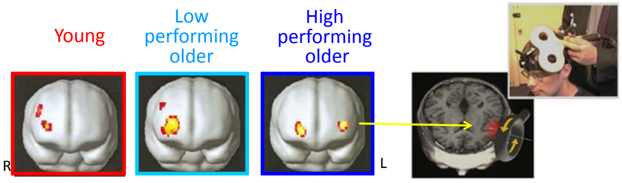




Davis et al., 2007
Memory and perception task

Compensatory mechanism in frontal cortex: Correlational or causal relationship?

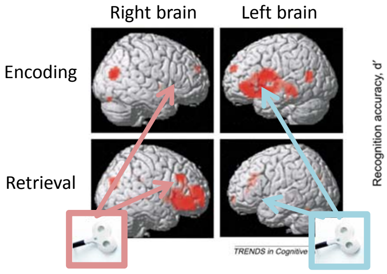
- Transient interference produced by repetitive transcranial magnetic stimulation (rTMS) to directly assesses causal relationships between performance and stimulated regions

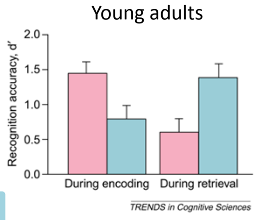


Cabeza et al., 2002
Source memory task

HERA and rTMS

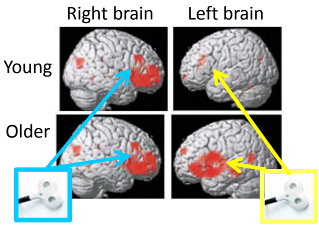
- The hemispheric encoding/retrieval asymmetry (HERA) (Tulving, 1994)

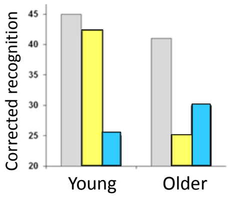




rTMS evidence for compensatory mechanism in frontal cortex: Rossi et al., 2004

- Visuospatial recognition memory during retrieval w/ rTMS
- Age-related differences during memory retrieval
  - ✓ Older: Bilateral frontal interference effects
- Engagement of the left frontal region compensates older adults' memory retrieval performance





Brain aging:
Neural mechanisms of age-related frontal over-activation

- Greater frontal activity w/ age is typically interpreted as being compensatory
  - ✓ Aging brain attempts to counteract neural decline by reorganizing its function
  - ✓ Compensate for older adults' optimal behavioral performance

- Greater frontal activity w/ age could reflect inefficient operation of cognitive process
  - ✓ Declined ability to efficiently recruit cortical regions related to the tasks
  - ✓ Interference and a major cause of some of the behavioral deficit observed in cognitive aging

Age-related frontal over-activation reflect inefficient operation of cognitive process

- High performing older adults show less bilateral activity than lower performers

Incongruent

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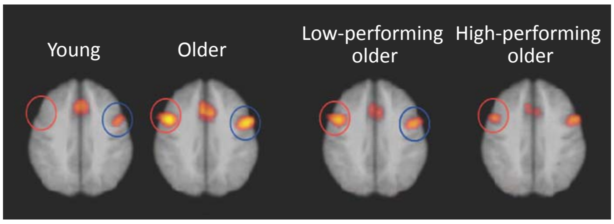
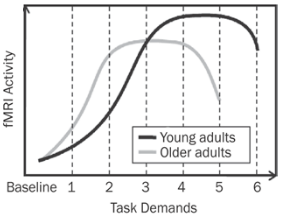


Flanker task
Colcombe et al., 2005

CRUNCH
Reuter-Lorenz & Cappell, 2008

- Compensation-related utilization of neural circuits hypothesis (CRUNCH)
- Level of task demands matters:
  - ✓ Older adults recruit more neural resources at lower levels of task demand for optimal performance (compensation), but reach a resource ceiling at higher level of task demand (inefficiency)



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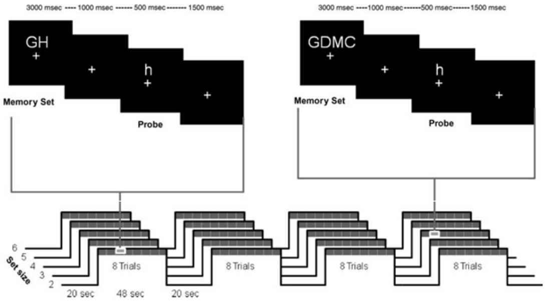
fMRI evidence for CRUNCH
Schneider-Garces, et al., 2009

- Sternberg working memory task (set size: 2-6)



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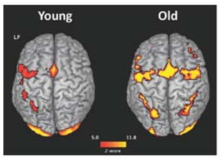
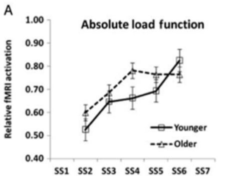
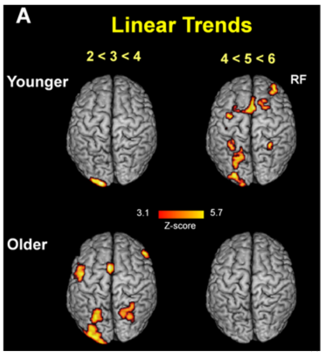
fMRI evidence for CRUNCH
Schneider-Garces, et al., 2009







Brain aging
Age-related changes in neural activity

- Reduced distinctiveness of neurocognitive representations ("De-differentiation")
  - ✓ Visual function: Within ventral visual cortex
  - ✓ Learning system: Medial temporal lobe (MTL) and striatum

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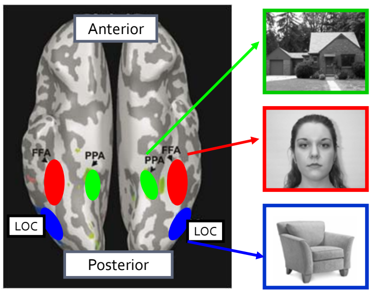
Ventral visual Cortex

- Different stimulus categories elicit different patterns of activity in ventral visual cortex



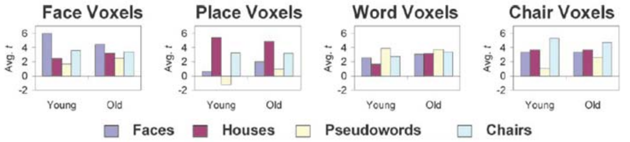
Place/House Areas (PPA)

Face Areas (FFA)

Object Areas (LOC)

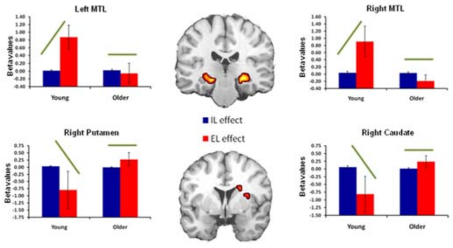
Brain aging
Age-related changes in neural activity

✓ Dedifferentiation of responses to different categories of visual stimuli (Park et al., 2004)



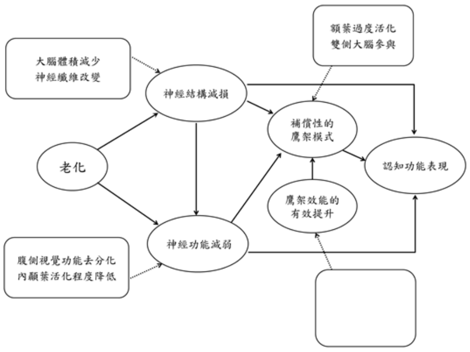
Brain aging
Age-related changes in neural activity

✓ Dedifferentiation across learning system (Dennis & Cabeza, 2011)
- Young: more activity in the medial temporal lobes (MTL) for explicit learning (EL) and more activity in the striatum for implicit learning (IL)
- Older: equivalent activation in these regions during the two tasks



Scaffolding theory of aging and cognition

Park & Reuter-Lorenz, 2009



Looking after the aging brain

Stay intellectually engaged
At best, mental activity seems to protect against age-related declines and progression to Alzheimer's disease. At worst, it increases an individual's baseline level so that age-related declines begin to affect everyday functioning later in life[12,128–130]. Enriched environments stimulate neurogenesis in aged rats, indicating a possible mechanism for the benefits of cognitive stimulation[131].

Maintain cardiovascular physical activity
Exercise aids executive function[132], reduces declines in tissue density in frontal, parietal and temporal cortex[133], and might have global effects on the brain[134].

Minimize chronic stressors
Proneness to distress, measured by the personality trait of neuroticism, is associated with increased risk of Alzheimer's disease and a faster rate of cognitive decline[135]. Increased glucocorticoid levels, which accompany stress, might damage hippocampal neurons over the lifespan[136]. Cortisol administration reduces glucose metabolism in the hippocampus in normal older adults[137].

Maintain a brain-healthy diet
A diet that is high in poly- and mono-unsaturated fatty acids (as found in fish and olive oil)[138,139], vitamin E (REF. 140) and polyphenols and antioxidants (found in citrus and dark-skinned fruits and vegetables)[141] might slow cognitive decline and prevent progression to Alzheimer's disease.

Hedden & Gabrieli, 2004

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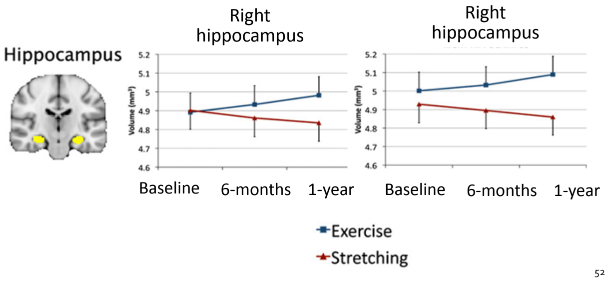
Scaffolding enhancement

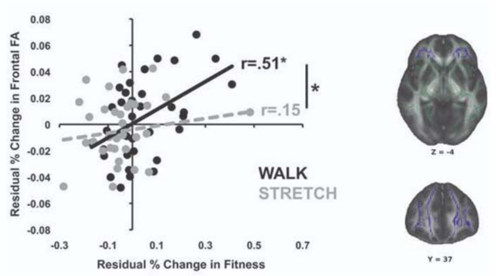
A case of aerobic fitness training

- Aerobic fitness increases size of hippocampus (Erickson et al., 2011)



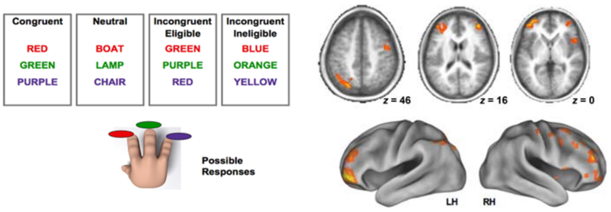
Scaffolding enhancement
A case of aerobic fitness training

- The beneficial impact of aerobic fitness on white matter integrity (Voss et al., 2012)



Scaffolding enhancement
A case of aerobic fitness training

- Higher level of aerobic fitness is associated with increase in prefrontal and parietal activations (Prakash et al., 2011)



Conclusions

- Cognitive changes in adulthood are multidimensional: decline and preserved
- Decreases in brain structure size and white matter integrity across the lifespan
- Functional brain ages in a dynamic way, declining in some respects but maintaining the ability to engage adaptive neural functions even in advanced age
- Pervasive increased frontal activation with age engages in compensatory scaffolding in response to the challenges posed by declining neural structures and function
- Scaffolding could be protective of cognitive function in the aging brain

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Thanks for your attention