

Neuroplasticity and Cognitive Aging

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Objectives

- To deepen your understanding of cognitive symptoms in middle-aged and old patients.
- Improve the quality of information provided to patients regarding neurocognitive symptoms and potential interventions for preserving and improving cognition.

Outline

- Cognitive function in healthy aging
- Cognitive function and dementia
- Neuroplasticity and aging
- Maintaining a healthy brain in old age

Longitudinal Changes in Specific Functions

Park DC et al. Psychol Aging 2002; 17:299-320

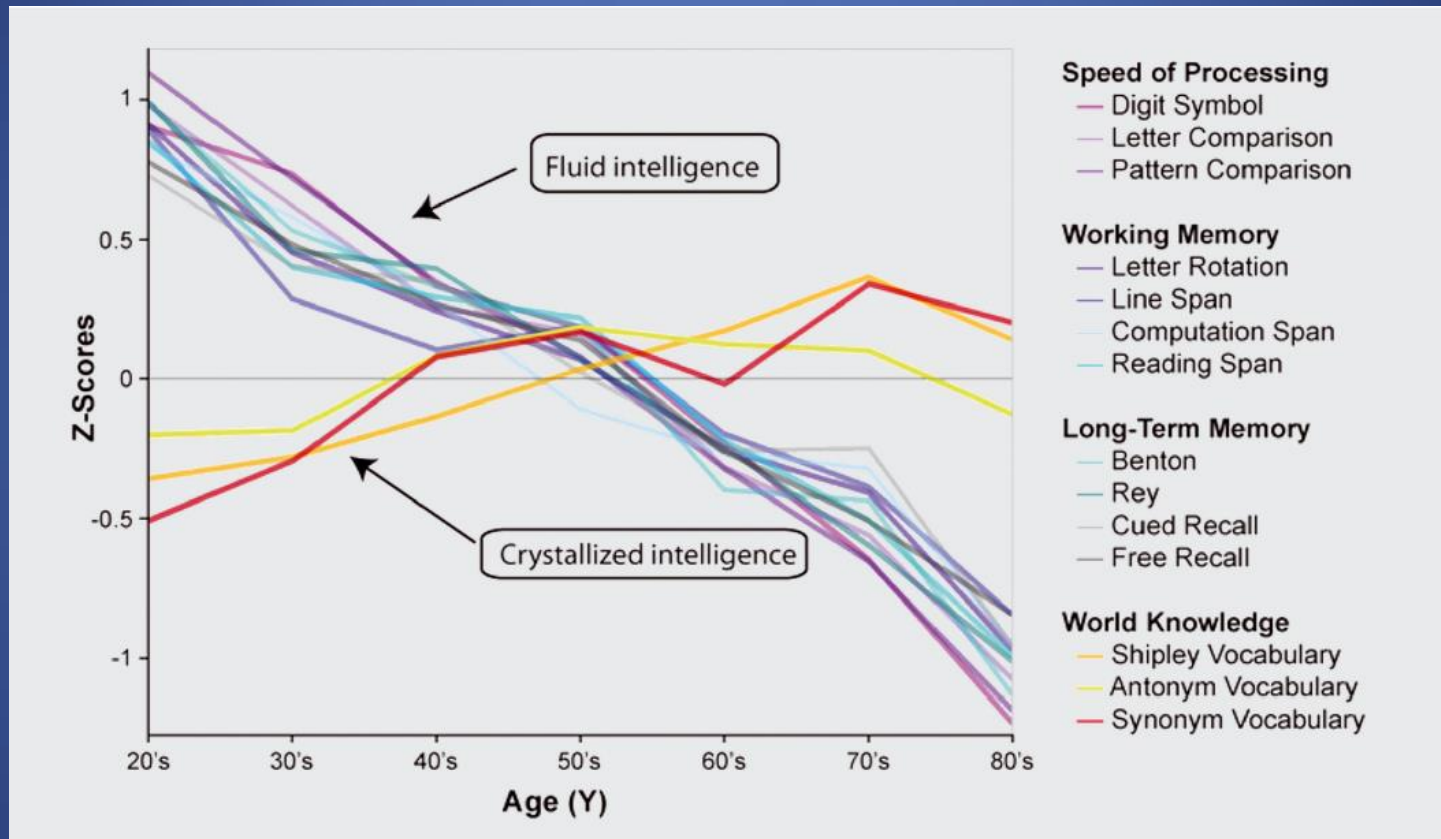


Figure 1. Cross-sectional aging data adapted from ref 9 showing behavioral performance on measures of speed of processing (ie, Digit Symbol, Letter Comparison, Pattern Comparison), working memory (ie, Letter rotation, Line span, Computation Span, Reading Span), Long-Term Memory (ie, Benton, Rey, Cued Recall, Free Recall), and world knowledge (ie, Shipley Vocabulary, Antonym Vocabulary, Synonym Vocabulary). Almost all measures of cognitive function (fluid intelligence) show decline with age, except world knowledge (crystallized intelligence), which may even show some improvement.

Memory: Age Effects

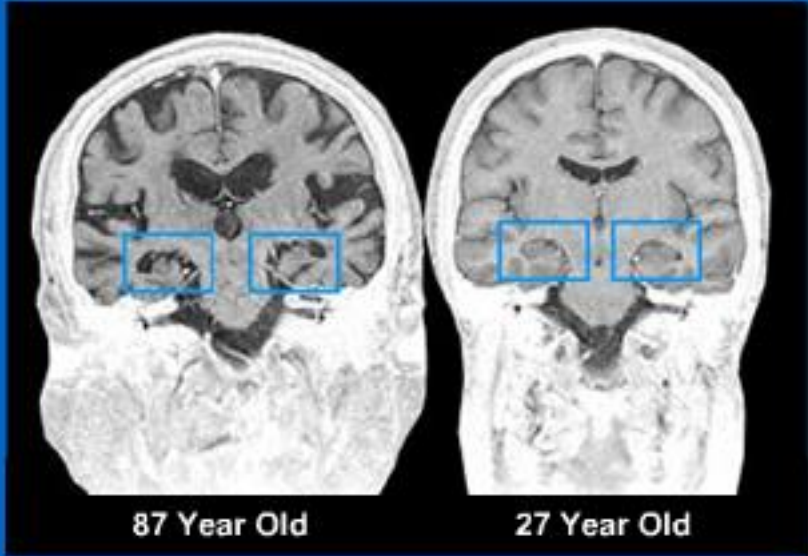
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	Description	Age effects
Working memory	information for rapid access	moderate decrease
Remote memory		
- <i>implicit</i>	instinct	increases
- <i>procedural</i>	know-how	increases
- <i>autobiographical</i>	personal knowledge	preserved
- <i>semantic</i>	general knowledge	increases
Recent memory		
- <i>episodic</i>	events	<u>decreases: most affected</u>
- <i>prospective</i>	remember to do something	decreases

Episodic Memory


- Ability to recall specific recent events
- Most sensitive type of memory to brain damage and aging
 - Aging affects encoding, storage and retrieval of this information
- Degree to which age affects types of episodic memory:
 - Free recall > cued recall > recognition recall

Hippocampus: Where Episodic Memory is Born



87 Year Old 27 Year Old

The **hippocampus** is the memory center of the brain. There is some cell loss associated with healthy aging, but this by itself does not indicate significant memory loss.



What's Normal?

- What's his name?
- What's that called?
- Where did I park?
- Where did I put those?
- Did I tell you this already? Yes.
- Did I ask this already? Yes.
- Did you tell me this already? Yes.

What's Not Normal

- Getting lost in a familiar place.
- Not being able to follow directions/a recipe
- Telling the same story more than twice without asking.
- Asking the same question more than twice.
- Losing interest in conversation, leaving home, hygiene, other people

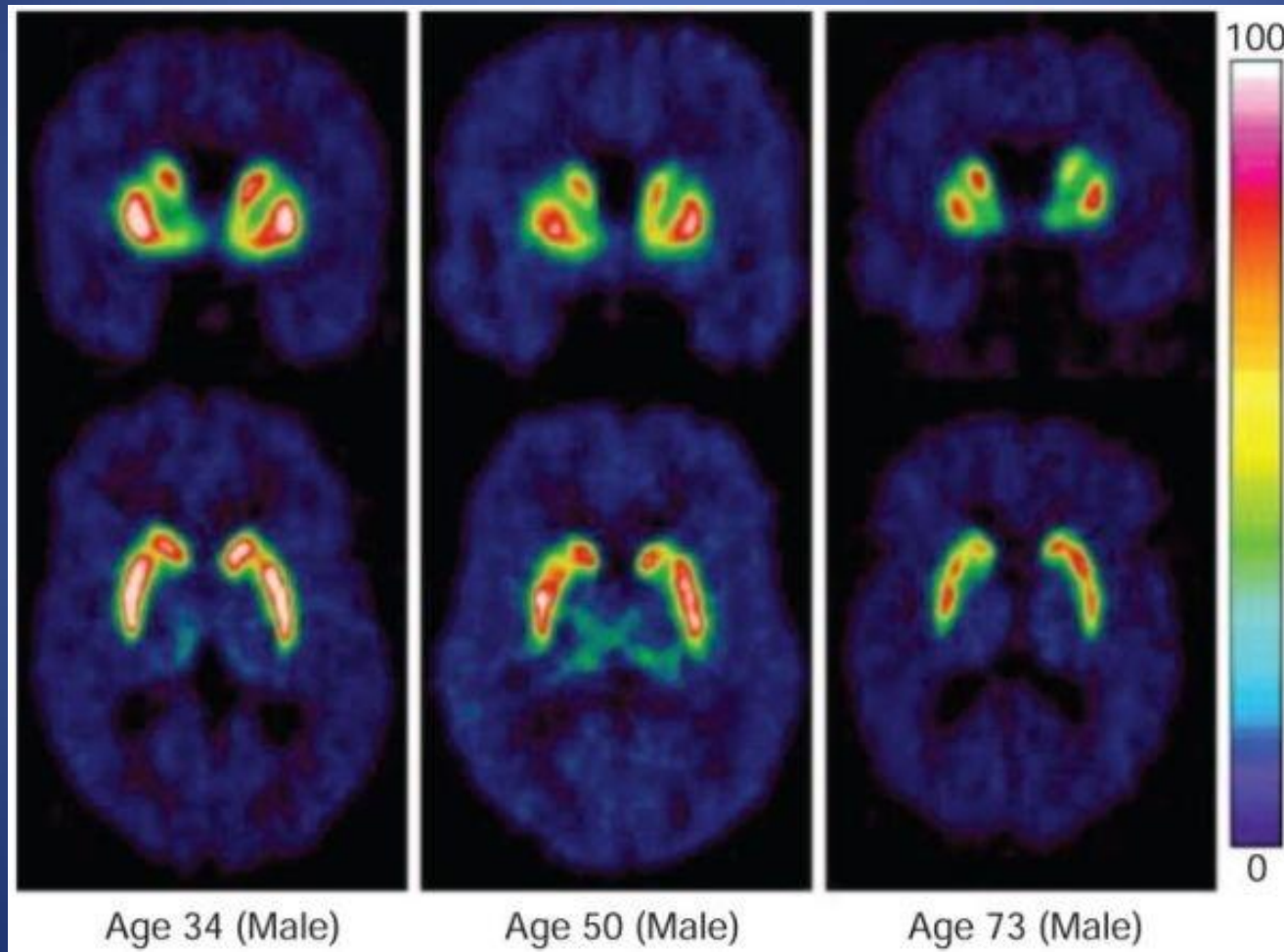
Attention:

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Does Aging Cause ADD?

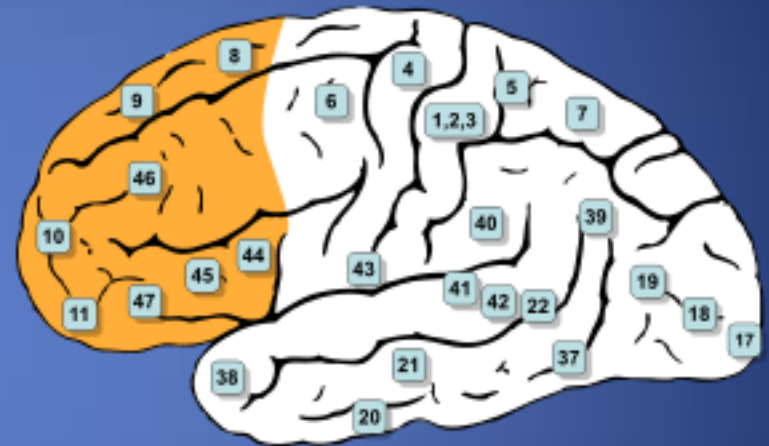
	Description	Age Effects
Selective attention	Ability to focus despite distractions	slight decrease
Divided attention	Multi-tasking	decreased
Attention switching	Ability to switch from one task to another	much reduced
Sustained attention	Ability to concentrate	no effect

Dopamine and Attention



Mindfulness Helps Memory

- Hippocampus encoding is aided by prefrontal cortex
- Greater awareness and specific efforts to focus attention will improve episodic memory
- “Top down processing”
 - Greater PFC activation in older adults trying to form “source memories” (who, where, when).
Dennis NA et al. J Exp Psych: Learning Memory and Cognition 2008; 34:4:791-808



Executive Control

- Prefrontal cortex (PFC) is the “conductor of the orchestra”
- PFC integrates multiple other brain regions with specialized functions
- Serves decision-making
- Impairment indicates pathology
 - Attention and speed-based tasks the exception

Sensory Perception

- Hearing and vision bring information that help encode memory
- Impairment in sensory function requires special effort to interpret perceptions
- Special efforts draws attention away from other aspects of experience
- Difficulty in interpretation may lead to resignation, inattention and isolation

Hearing Loss and Dementia

Lin FR et al. Arch Neurol 2011; 68:2:214-20

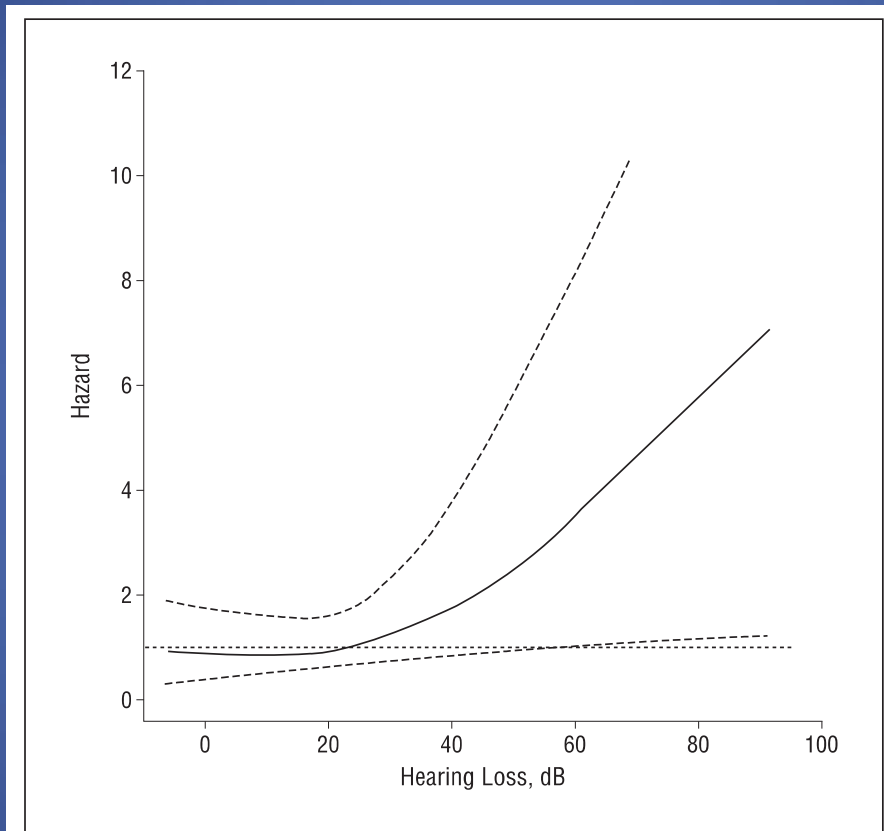


Figure 2. Risk of incident all-cause dementia by baseline hearing loss after adjustment for age, sex, race, education, diabetes mellitus, smoking, and hypertension. Hearing loss is defined by the pure-tone average of thresholds at 0.5, 1, 2, and 4 kHz in the better-hearing ear. Upper and lower dashed lines correspond to the 95% confidence interval.

Cognitive Changes

Salthouse TA. Current Direct Psychol Sci 2004; 13:4:140-44

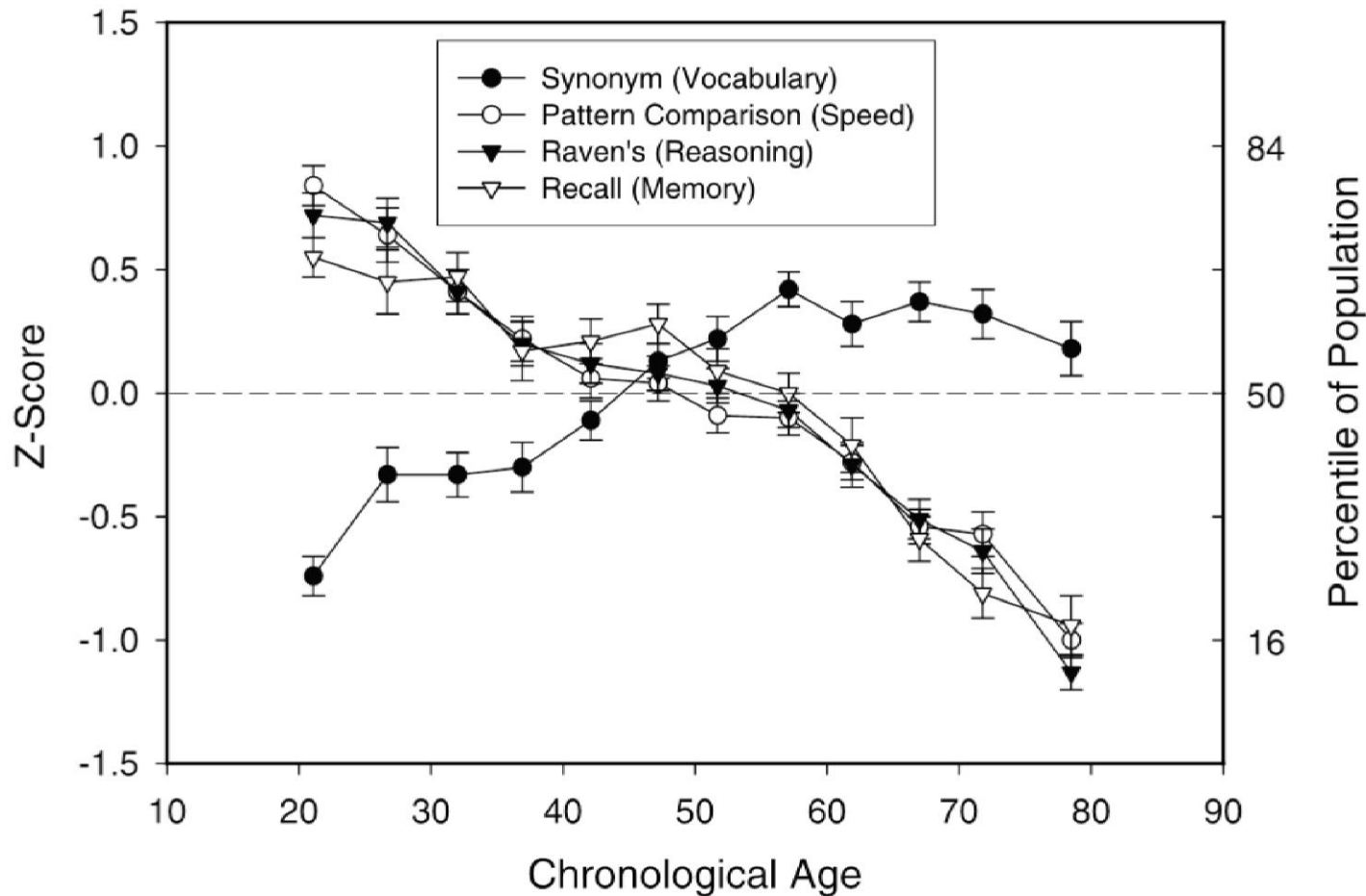


Fig. 1. Means (and standard errors) of performance in four cognitive tests as a function of age. Each data point is based on between 52 and 156 adults.

Cognitive Changes

Salthouse TA. *Current Direct Psychol Sci* 2004; 13:4:140-44

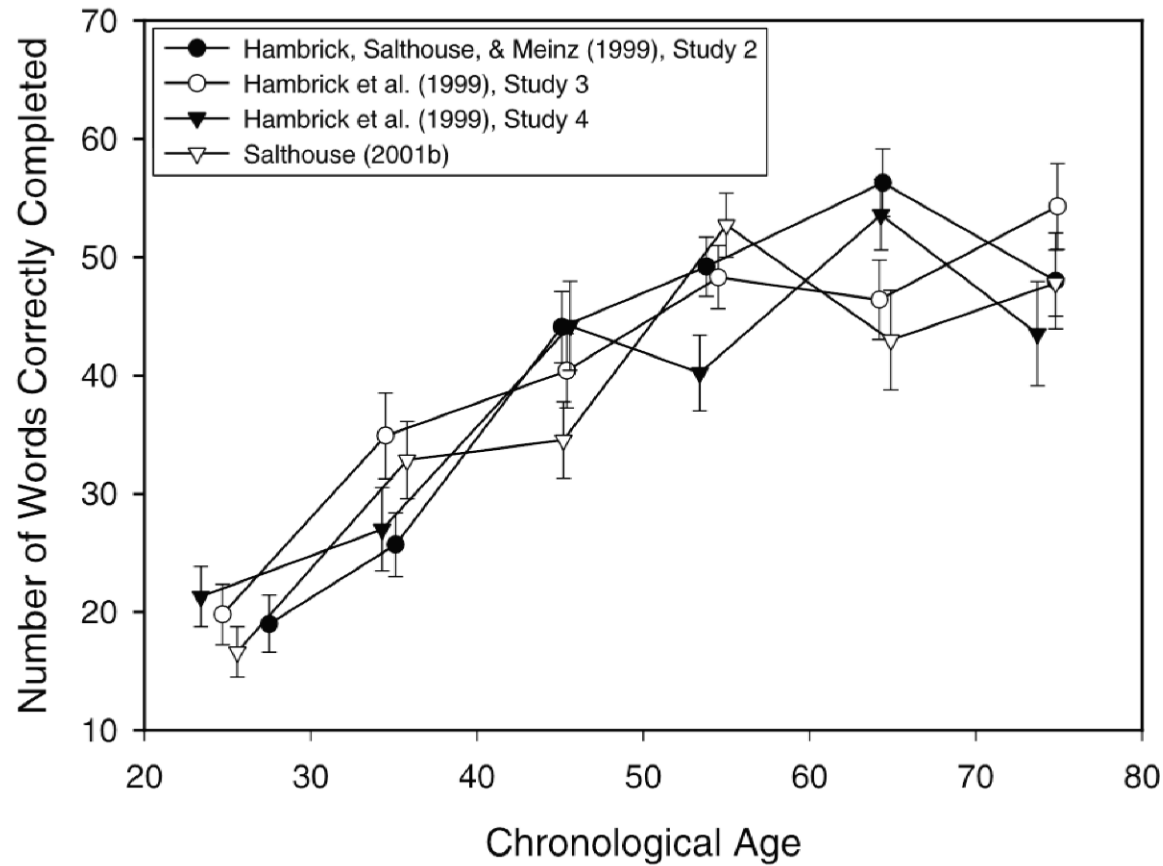


Fig. 2. Means (and standard errors) for the number of words in a *New York Times* crossword puzzle correctly answered in 15 min as a function of age. Between 195 and 218 adults participated in each study. The crossword puzzles required either 76 or 78 words for their solutions.

Speech and Language: Age Effects

- Vocabulary increases
- Skilled conversationalists
 - Stories contain more elaboration/embellishment
- Word retrieval is slowed
- Hearing loss:
 - may make conversation one-sided
 - requires contextual interpretation to compensate

Decision Making

- Reasoning, judgment, insight and wisdom increase with age
- Learning from experience, evaluating context and drawing from knowledge of history
- Dependent on prefrontal cortex
- Impairment indicates pathology

Wisdom

- Involves compassion, deep understanding and acceptance
- Involves factual knowledge, procedural knowledge and contextual knowledge
- Involves affect and impulse regulation

Compensatory Mechanisms

- Older adults activate more brain area to accomplish the same task
- Older adults employ wisdom of experience to do things more efficiently
- Older adults economize their energy to focus on the most important elements of tasks and work at their peak times

Variability in Cognitive Trajectory

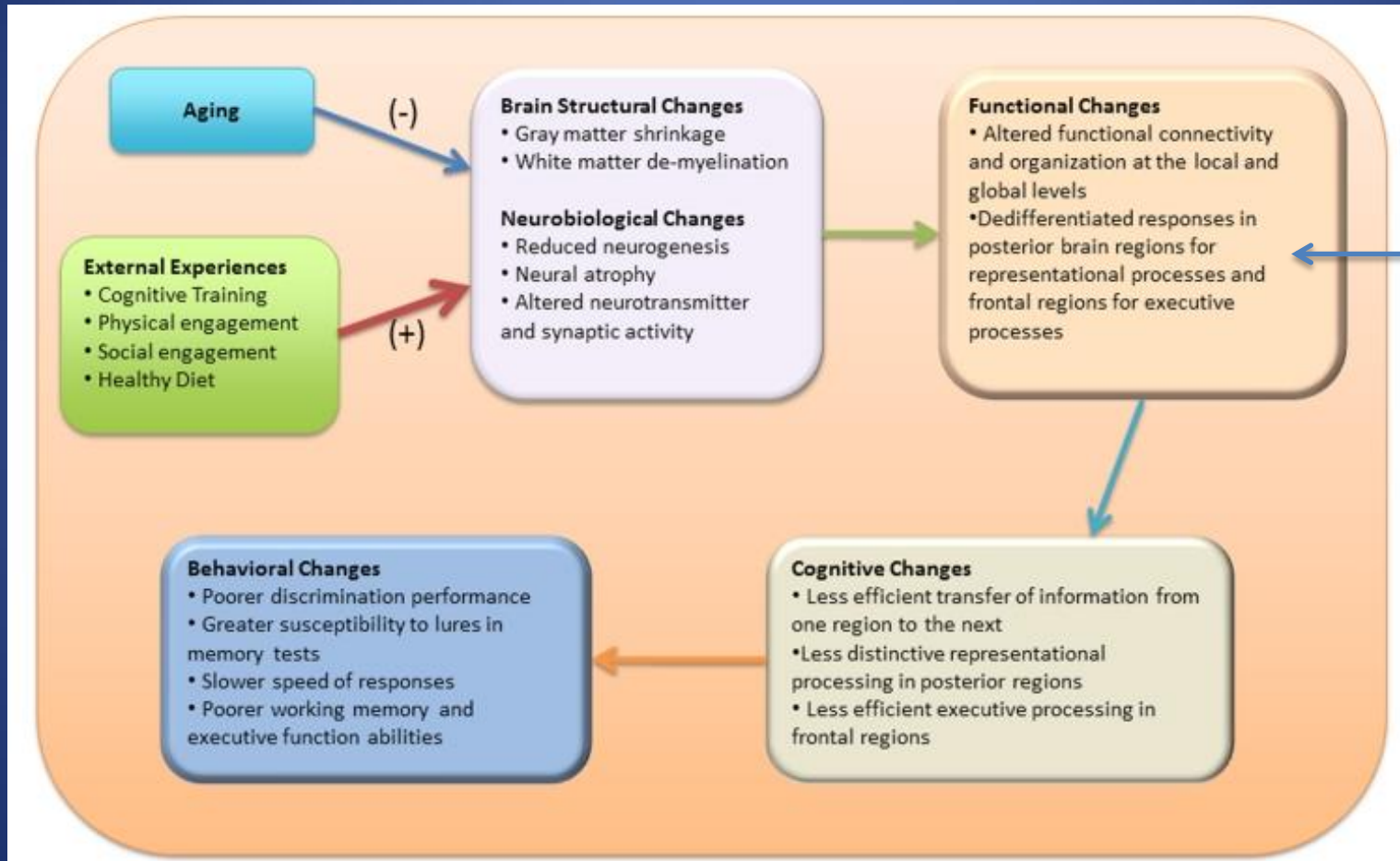
- Genetics
- Environment
- Lifestyle
- Illness
- Alertness
- Compensatory mechanisms



Cognitive Reserve

- Greater cognitive resilience and redundancy: more neurons and synaptic connections
 - Increasing CR through neuroplastic adaptation
 - Advanced education, high intelligence, physical, social and cognitive demands
 - Decreasing CR through negative adaptation:
 - (depression, stress, EtOH, TBI, sleep deprivation, vascular risk factors, etc.) increase risk of dementia
 - Delaying onset of dementia by 5 years has been estimated to prevent 50% of cases

A Cascade of Decline



Risk Factors For AD

Patterson C et al. CMAJ 2008;
17:5:548-56

Table 2: Risk of Alzheimer disease by apolipoprotein E genotype³

Genotype	Odds ratio (95% CI)*
ε3/ε3	1.0 [ref]
Single ε4	3.2 (2.9-3.5)
ε4/ε4	11.6 (8.9-15.4)
ε2/ε3	0.6 (0.5-0.8)

Note: CI = confidence interval, ref = reference group.

*Compared with white people, the strength of the association is weaker among black and Hispanic people and stronger among people of Japanese descent. The association is stronger among women than among men.

Table 1: Risk factors for Alzheimer disease

Factor	Risk (95% CI)
Systolic hypertension > 160 mm/Hg	RR: 1.5 (1.0-2.3) ⁴ OR: 2.3 (1.0-5.5) ⁵
Serum cholesterol > 6.5 mmol/L	RR: 2.1 (1.0-4.4) ⁵ RR: 3.1 (1.2-8.5) ⁶
Moderate wine consumption (250-500 mL/d) compared with more or less than this amount	RR: 0.53 (0.3-0.95) ⁷
High level of physical activity* compared with little or no regular exercise	RR: 0.5 (0.28-0.90) ⁸ RR: 0.55 (0.34-0.88) ⁹ RR: 0.69 (0.5-0.96) ¹⁰
Smoking, current	RR: 1.74 (1.21-2.50) ¹¹ RR: 1.99 (1.33-2.98) ¹²
Head injury, with loss of consciousness	
Moderate	HR: 2.32 (1.04-5.1) ¹³
Severe	HR: 4.51(1.77-11.47) ¹³
Education > 15 yr (v. < 12 yr)	RR: 0.48 (0.27-0.84) ¹⁴
Statin drugs	RR: 0.82 (0.46-1.46) ¹⁵ HR: 1.19 (0.35-2.96) ¹⁶
Nonsteroidal anti-inflammatory drugs	RR: 0.42 (0.26-0.66) ¹⁷ RR: 0.51 (0.37-0.70) ¹⁸

Note: CI = confidence interval, RR = relative risk, OR = odds ratio, HR = hazard ratio.

*See section on lifestyle factors for details about physical activity.

Psychosocial Factors

- Lowered expectations
- Self-selected reduction in novel environments and tasks
- Reduced schedule of activities
- Negative learning leading to withdrawal

Can We Prevent Cognitive Decline?

Neuroplasticity in Old Age

Park DC and GN Bischof. Dialogues in Neurosci 2013; 15:109-119

- Best evidence comes from stroke literature
 - Adaptive changes in healthy brain regions to regain function
- Requires placing exceptional demands
 - MRI volumetric study of London cabbies vs. bus drivers- regional specialization
- Extensive animal literature and emerging prospective evidence in humans

Neuroplasticity

- Change in brain structure and function in response to environment and experience.
 - Occurs at both synaptic, network and anatomic levels.
 - Neurons that are actively stimulated, survive
 - Neuronal networks that are not active, atrophy
 - Neuronal networks that are frequently stimulated tend to become autonomously active, default mode network
 - Activity-dependent neuronal network development and refinement results from production of neurotrophic factors

Neurotrophic Factors

Rothman SM and Mattson MP. Neuroscience 2013; 239:228-40

- Maintenance and adaptive remodeling of neuronal networks in adults depends on:
 - Neurotransmitters and trophic factors (nerve growth-promoting proteins)
 - BDNF production stimulants of other proteins that promote adaptation, learning, neurogenesis
 - Process shut down by cortisol (stress)
 - Promoted by physical exercise, cognitive exercise, brief fasting, environmental enrichment, antidepressants, ECT

Activity-Dependent Neuroplasticity

Rothman SM and MP Mattson. Neuroscience 2013; 239:228-240

- Interactions between neurotransmitter-dependent neuronal activation and trophic proteins (e.g. BDNF) produce adaptive changes in synaptic connectivity
- Exercise and cognitive demands increase neurogenesis and neuronal resistance to oxidative, metabolic and proteotoxic stress
- Insufficient exposure to stimulatory activity or excessive exposure to proteotoxic hormones result in less BDNF production and less resistance to degenerative change

Good Stress: Caloric Restriction and Exercise

from Rothman and Mattson Neurosci 2013

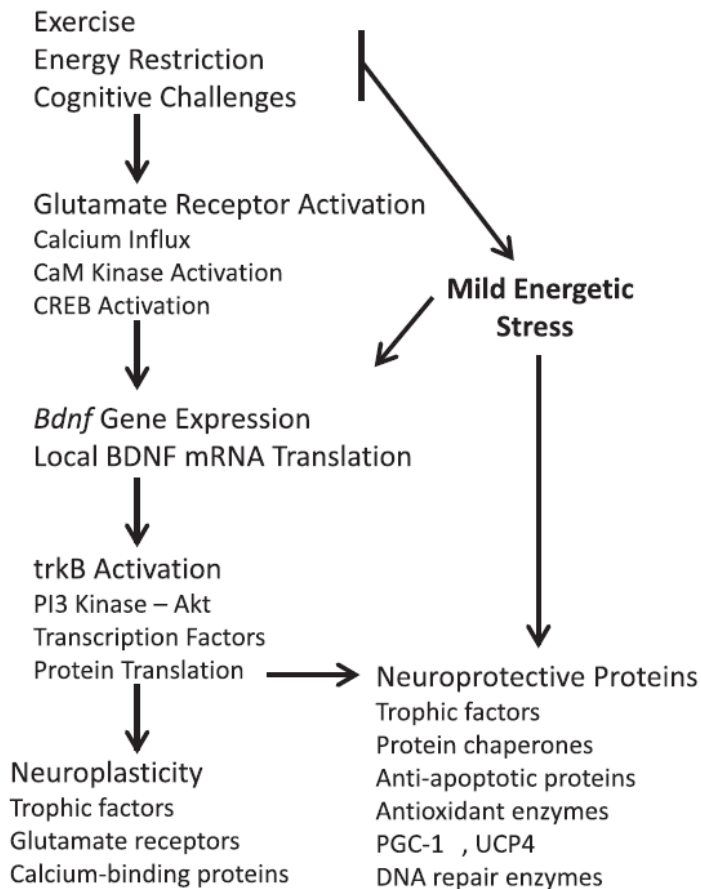


Fig. 1. Central roles for BDNF in the beneficial effects of exercise, dietary energy restriction and cognitive challenges on brain health. Vigorous intermittent exercise, energy restriction and cognitive challenges activate excitatory neuronal circuits that employ glutamate at their synapses. Glutamate receptor activation results in calcium influx and activation of calcium/calmodulin (CaM)-dependent kinases. CaM kinases can stimulate local translation of BDNF mRNA in dendrites, and can also activate the transcription factor CREB which induces the expression of the *Bdnf* gene. BDNF activates high affinity receptors (trkB) in both the neuron in which it is produced and in adjacent neurons. Activated trkB engages the PI3 kinase–Akt kinase pathway which up-regulates the production of the indicated proteins involved in neuroplasticity (synaptic plasticity and neurogenesis) and neuroprotection. BDNF-independent adaptive stress response signaling pathways are also activated by exercise, energy restriction and cognitive challenges.

Bad Stress

Rothman SM and Mattson MP. Neuromolecular Med 2010; 12:1:56-70

- Adverse stressors: Trauma, sleep deprivation, anxiety, depression, fear
- Chronic adverse stress in mouse models of AD accelerates cognitive decline and hippocampal atrophy
 - Increased A β deposition
 - Decreased neurogenesis
 - Increased apoptosis (cell death)
 - Reduced long-term potentiation
 - Reduced production of neurotrophic factors
 - Increased production of oxidative free radicals
 - Partly mediated through increased corticosteroids

BDNF and Major Depression

Lee BH and Kim YK. Psychiatry Investig 2010; 7:231-235

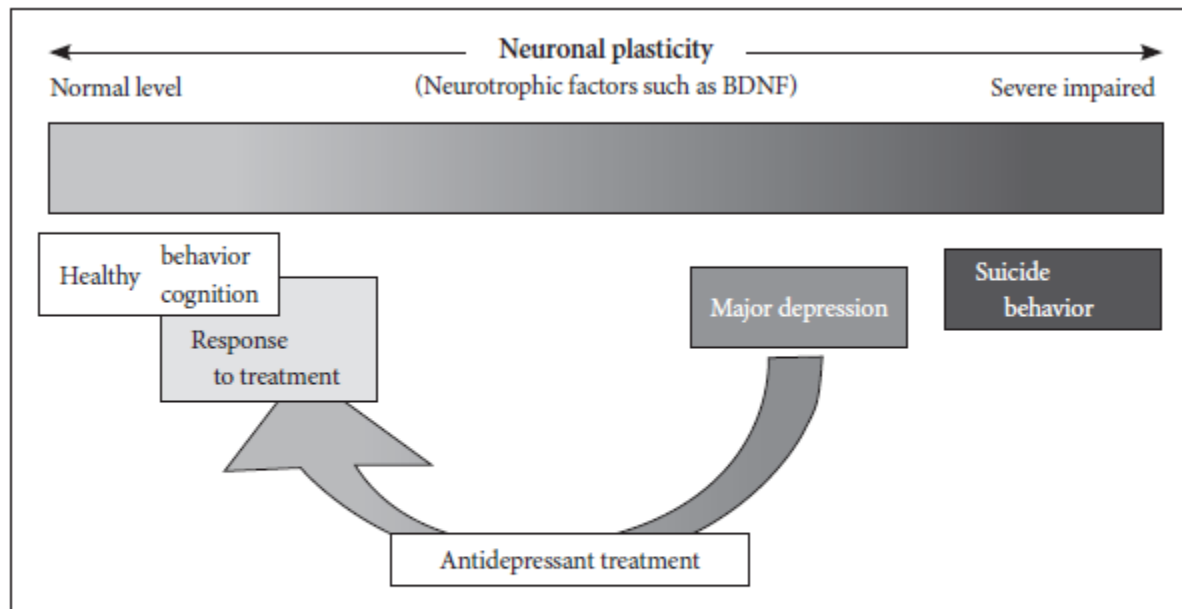
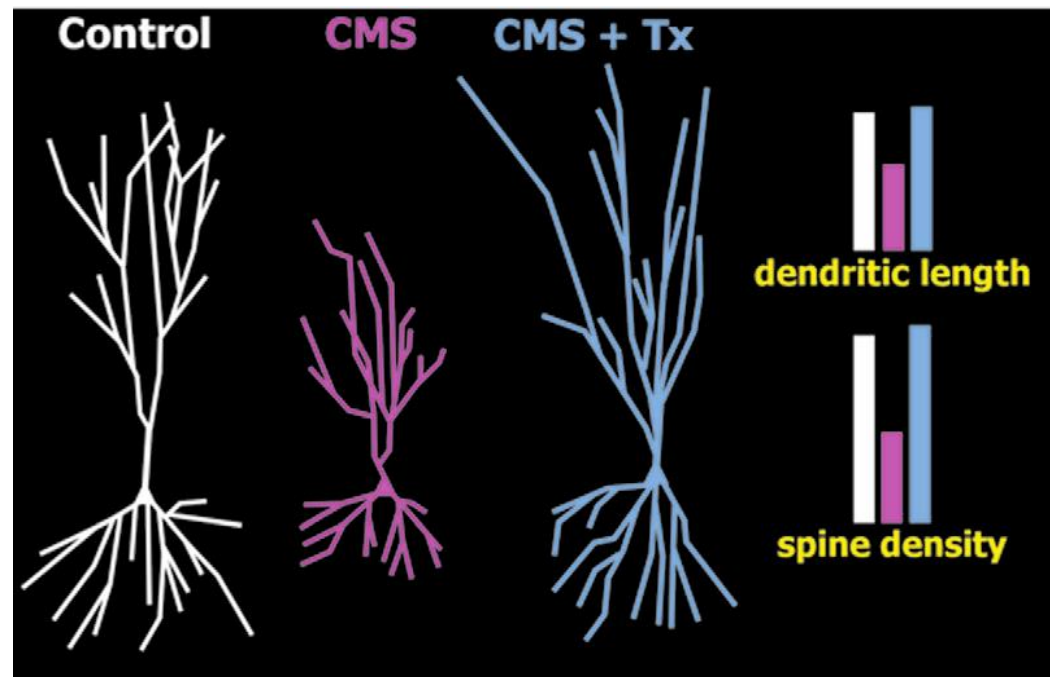


Figure 1. The neuronal plasticity in major depression, antidepressant treatment, and suicide behavior. Major depression is associated with impaired neuronal plasticity in the brain. Suicide behavior can be a consequence of very severe impaired neuronal plasticity. Antidepressant treatments promote several forms of neuronal plasticity, including neurogenesis, synaptogenesis and neuronal maturation together with increasing brain-derived neurotrophic factor activity, which can develop the antidepressant response. The neuronal plastic change can influence mood or recover depressed mood.

Effects of Stress on Neurons

Kays JL et al. J Neuropsychiatry Clin Neurosci 2012; 24:2:118-24

FIGURE 3. Exposure of rats to 6 weeks of unpredictable chronic mild stress (CMS; pink) induces depressive-like behaviors (e.g., anhedonia, learned helplessness) and multiple detrimental effects in the hippocampus and medial prefrontal cortex (mPFC), including decreases in neurogenesis, dendritic length, and synaptic density, as compared with control conditions (white). Both behavioral and structural deficits can be reversed by administration of antidepressants (Tx) during the final 2 weeks of CMS (CMS + Tx; blue).¹³ Schematic representations of mPFC neurons under the three conditions illustrate average dendritic changes. The authors of this study noted that these results were independent of neurogenesis, suggesting that restoration of normal dendritic length and synaptic density underlie behavioral recovery.



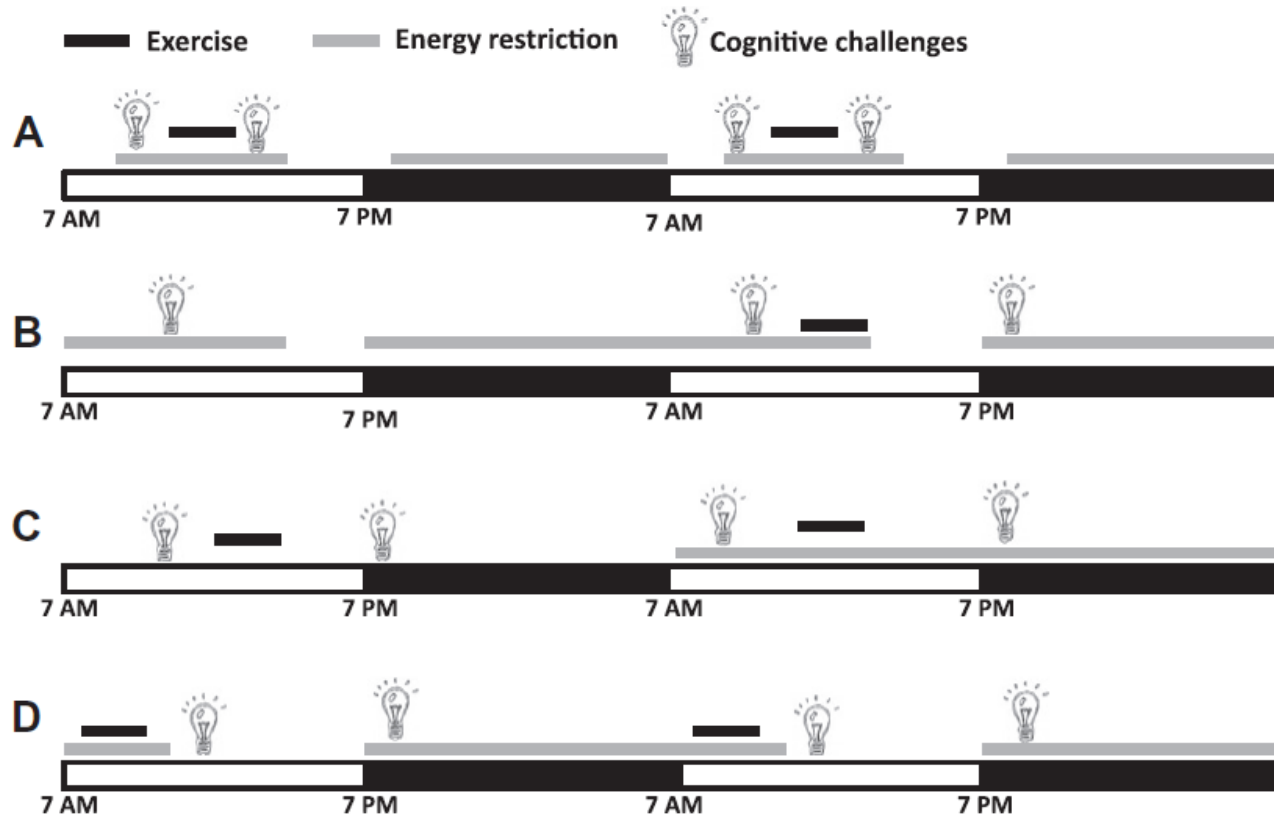


Fig. 2. Prescriptions for optimal brain health. Findings from studies of animal models and human subjects suggest that intermittent dietary energy restriction, exercise and cognitive challenges (the BFT) increase BDNF production and signaling, and can protect the brain against a range of neurological disorders including anxiety, depression, stroke, and Alzheimer's and Parkinson's diseases. Based upon existing knowledge from human studies we set parameters of the BFT as follows: exercise – at least 20 min of vigorous aerobic exercise; energy restriction – zero calories for restriction periods of 8–12 h, and no more than 600 calories for a 24-h restriction period; cognitive challenges – learning new concepts, integrating information, and generating new ideas. (A) Eat breakfast and dinner – do not eat lunch – exercise during midday – critical thinking and reading prior to and after exercise. Do this every day of the workweek. (B) During the workweek do not eat breakfast or lunch – eat in the early evening – exercise in the afternoon on Monday, Wednesday and Friday. (C) Exercise in the afternoon every other day – fast every other day – maintain intake of water or other non-caloric beverages. (D) On a daily basis: do not eat breakfast – exercise in the early morning – eat lunch and dinner.

Diminished Neuroplasticity w Age?

Luber B et al. Dialogues in Clin Neurosci 2013:15,87-98

- 5 days of low intensity *rTMS* induced hippocampal LTP in young but not old rats
- Less antidepressant effect from *rTMS* in elderly depressed patients
- Decreased LTP in hippocampus/MTL associated with greater memory impairment
 - Baliani M et al. Rejuvenation Res 2012:15, 235-238

“Lifestyle” and Brain Aging in Animals

Mora F. Dialogues Clin Neurosci. 2013; 15:46-52

- Enriched environments improves learning, enhances neurogenesis, increases brain weight, dendritic branching, synapse formation and neurotrophic factors
- Caloric restriction (20-40%) improves learning, dendritic branching and increased neurogen.
- Chronic stress accelerates hippocampal and frontal atrophy, decreases neurogenesis, dendritic branching and neurotrophic factors

Meditation and Neuroplasticity

Xiong GL and PM Doraiswamy. Ann NY Acad Sci 2009; 1172:63-69

- There is evidence that consistent meditation:
 - lowers cortisol, plasma lipids, free-radicals
 - Increases BDNF, gray matter and cognitive reserve
- Evidence is weakened by: small N, potential cohort effects, methodological differences: meditation technique, duration & frequency (“dose effects”), age of subjects, etc.

Dancing: The Essence of Successful Aging

Olsson CJ. *Frontiers in Neurosci* 2012; 6:155

Kattenstroth JC et al. *Front. Aging Neurosci.* 2010; 2:31

- Dancing combines cognitive, social and physical activation (all thought to preserve fx)
- Cohort study of long-term dancers vs. sedentary controls matched for age, gender and education.
- “Dancers” showed superior cognition in multiple domains, as well as better balance and sensorimotor function.
- Not good science, but I choose to believe!

Should U Sudoku?

Park DC and GN Bischof. Dialogues in Neurosci 2013; 15:109-119

- Strong evidence that practicing mental tasks improves abilities in those tasks even in old age
 - Benefits don't seem to generalize in older adults
 - Benefit in people with MCI/dementia not known
- There is evidence that the improvement is “durable”, lasting months, even for older adults
- New evidence that memory training may generalize to other “fluid” intelligence tasks in young but not old adults
 - Less neuroplasticity in older adults may mean less general benefit
 - Those with MCI/dementia may have even less ability to respond.....but cognitive engagement may have other benefits

Experience Corps Project

Carlson MC et al. J Gerontol A Bio Sci Med Sci 2009; 64:1275-1282

- Examined cognitive benefits to seniors who volunteered as teaching assistants for young children
- Data indicate improvements in morale and cognition including activation of prefrontal cortex and improvement in executive function tests
- Authors conclude: Immersion in “real world” activities may yield superior results to computer-based cognitive training: mood effect?

Exercise for Neuroprotection?

Ahlskog JE et al. Mayo Clin Proc 2011; 86:9:876-84

- Cross-sectional studies show less dementia, better cognition and less atrophy in more active older adults
- Exercise may enhance cognition in multiple ways.....but does it offer primary prevention of dementia?
- Questions: amount, duration, type, subject variables, applying animal data
- Outcome measures: cognition, functional MRI, PET, anatomic MRI

Physical Exercise and Cognitive Aging

Ahlskog JE et al. Mayo Clin Proc 2011; 86:9:876-884

- Exercise associated with lower dementia risk (RR=0.72) in 10 of 11 prospective cohort studies
- Potential mechanisms
 - Reduced vascular risk and increased blood flow
 - Direct neurotrophic effect : Exercise \uparrow BDNF, IGF-1, and turning on synaptic plasticity genes
 - Enhanced long term potentiation (new learning)
 - Improved mood and well being

Physical Exercise and Cognitive Aging

Ahlskog JE et al. Mayo Clin Proc 2011; 86:9:876-884

- Fitness (peak VO_2) associated with greater brain volume
- Animal and human studies indicate improved hippocampal volumes and spatial memory from aerobic exercise
 - 150 min/week moderate intensity
- Resistance exercise may improve cognition for > 1 year after 12 mo. Intervention
- Plasma BDNF levels correlate with cognition in healthy seniors and are lower in AD
- BDNF may be increased by exercise in some studies (both short bursts and long endurance)
- AD biomarkers may decrease w/exercise
 - Liang KY et al. Ann Neurol 2010; 69:161-173

Exercise for Neuroprotection?

Smith PJ et al. Psychosomatic Med 2010; 72:239-52

- Meta-analysis of 29 RCT in subjects without dementia, aerobic exercise for 1-18 mos.
- Modest improvement in memory, attention, processing speed and executive function
- Mechanism? Can't distinguish primary neuroprotection/neuroplastic from mood, vascular or metabolic effects

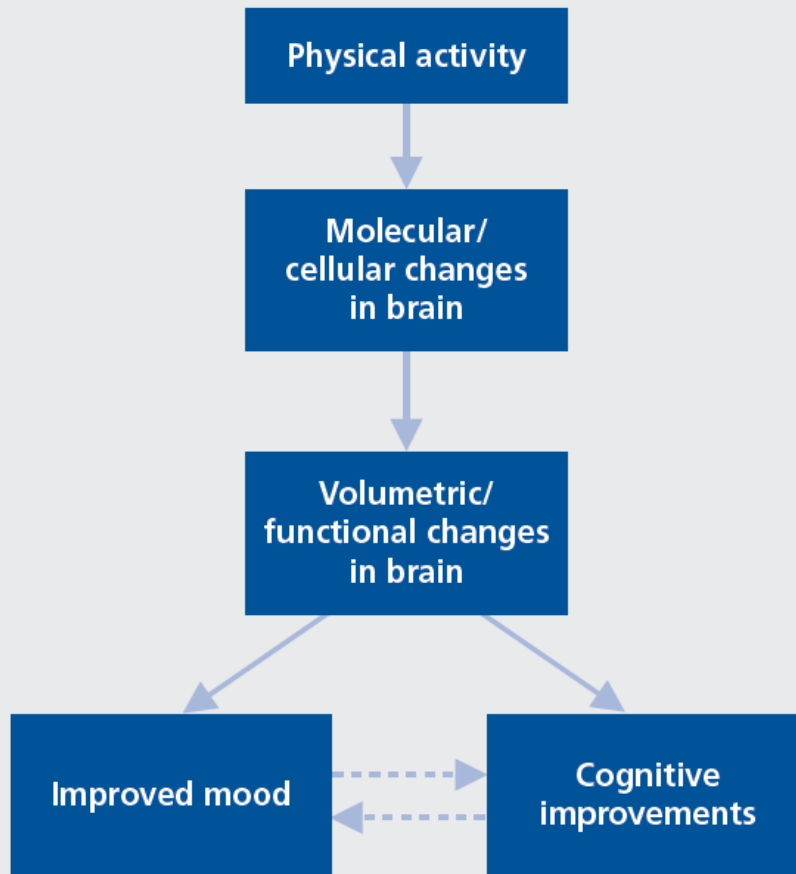
Is Exercise Neuroprotective?

- 6 mo. RCT in healthy seniors with aerobic regimen, improved cortical activation and “connectivity”
 - Colcombe SJ et al. Proc Nat Acad Sci 2004; 101:3316-21
- 12 mo. RCT comparing aerobic vs. nonaerobic exercise (stretching, strengthening), both groups improved *fMRI* activation and connectivity
 - Voss MW et al. Frontiers Aging Neurosci 2010; 2:pii.32

Does Exercise Slow Dementia?

Ahlskog JE et al. Mayo Clin Proc 2011; 86:9:876-84

- RCT studies of increased exercise (aerobic and resistance) in MCI have not shown consistent increases in BDNF levels
- Recent small study showed trend for less β -amyloid in MCI subjects after 6 mos. Of exercise compared to sedentary controls
- Several studies have shown good effects of exercise on memory and biomarkers (β -amyloid and tau) in transgenic mice



Erickson KI et al.
Physical activity and brain
plasticity in late adulthood.
Dialogues in Clin Neurosci
2013: 25:99-108.

Figure 1. A schematic representation of the general path by which cognitive function and mood are improved by physical activity. It could be hypothesized that improvements in cognitive function mediate the improvements in mood or that improvements in mood mediate some of the improvements in cognitive function. The dotted lines represent these hypothesized paths.

Prescribing Exercise

Ahlskog JE et al. Mayo Clin Proc 2011; 86:9:876-84

- Better evidence for aerobic exercise at improving and maintaining cognition in healthy seniors
 - 30 minutes of moderate intensity, 5 d/wk?
 - 20 minutes vigorous exercise, 3 d/wk?
- Insufficient evidence for resistance training for cognition, although may be very important
- Threshold or graded effects? A little may be better than nothing.
- Challenges for developing routines in people with physical limitations, limited resources
- Is it too late in dementia patients? Never too late (at least for mood and morale).

Summary

- Cognitive training may provide persistent but specific effects, whereas caloric restriction, social and physical activities may provide more general cognitive and emotional benefits
- In newly diagnosed MCI or dementia patients, prescribe fruits and vegetables, exercise and social engagement, *although any benefit may only be through general health, mood and sense of well being.*