Minding the Mind as We Age
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Talk Outline

- Common memory complaints
- Normal Brain Aging: Changes in structure and function
- Plasticity and Cognitive Reserve
- Threats and opportunities in optimal aging
- The Seven Commandments
- Cognitive enhancement
Top 7 Memory Complaints

Hi. I'm, I'm, I'm….. You'll have to forgive me. I'm terrible with names.

Namenesia
Wordmnesia

THIS MODERN WORLD by TOM TOMORROW

UNCH’ looks like Bill’s been forgetting to take his memory enhancement pills!

Dang! What was I going to say?

It was right on the tip of my... say...

You know, that thing in my mouth...

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Roomnesia

Now why did I come in here?
I can never remember where I put things.

Episodic Fleeting Thought Syndrome

What the heck was I about to say?....???
Parkingmnesia
(Shopping Mall type)

I think it was in Section GG-17… or was it DD-71?

Paroxysmal A-Navigationalism

I’m getting the feeling we missed the exit for Revere
The Brain: Normal Aging

Shrinkage!
Aging and Brain Structure

- Gray volume
- Number of neurons
- Neuronal density
- Neuronal features (e.g., size, pigment acquisition, dendrites)
- Synaptic density
- White matter volume and integrity
- Ventricular size

Oregon Brain Aging Study

[Images of brain scans comparing 87-year-old to 27-year-old brains, highlighting specific regions]
100 billion neurons

Mouse – CA1 Hippocampal Pyramidal Neurons

Up to 200,000 synapses per neuron

Mouse – CA1 Hippocampal Pyramidal Neurons
Aging and Neurochemistry

- ↓ Dopamine
- ↓ Acetylcholine
- ↓ Norepinephrine
- ↓ Serotonin
- ↓ NMDA receptors (but not AMPA or kainate)
- ↓ Cholinergic receptors
PET: Age related decline in dopamine transporter availability

Erixon-Lindroth N. et al. The role of the striatal dopamine transporter in cognitive aging. Psychiatry Res. 2005; 138

Communication in the aging brain

- ↓ number of synapses
- ↓ density/functionality of receptors
- ↓ availability of key neurotransmitters
- White matter pathways develop lesions
- “Silent” focal cortical lesions
How about some good news?

Plasticity

- Changes that occur due to learning and experience
- Normal development
- Shift of functional organization after injury
- Synaptic pruning in aging – elimination of weak synapses
- Apoptosis (programmed cell death) – relinquishing cell after purpose is served
- Neuronal change (structure, synapses)
- Neurogenesis
Neurogenesis and Plasticity

- **THEN**: The brain is equipped with a finite complement of neurons. Once a neuron dies, it is never replaced. Therefore aging entails a relentless, subtractive process.

- **NOW**: The change in the absolute number of neurons is not significant. New neurons sprout in the hippocampus throughout the lifespan.

PET Brain Activity during Source Memory Task

**Young**

**Old-Low**

**Old-High**

- Old-Low performing subjects recruited similar PFC regions as young adults but used them inefficiently.
- Old-High performing subjects compensated for age-related memory decline by reorganizing the episodic retrieval network.

→ SUPPORTS COMPENSATION VIEW OF HAROLD
  Hemispheric Asymmetry Reduction in Old Adults

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Cognitive Reserve

Yaakov Stern

- Relationship between brain pathology and cognitive effect is moderated by CR.
- CR composed of genetic and acquired (environmental) factors.
- CR markers: education, occupation, leisure interests.
- Greater CR → less impact on function with similar level of pathology.
- Greater CR → Steeper decline once pathology overwhelms.
- Neurophysiologic substrate?
Aging Scorecard

**Bad News**
- Degradation of cortical/subcortical networks
- ↓ Redundancy
- ↓ Connectivity

**Good News**
- Plasticity
- Compensation
- Reserve

The spectrum of small vessel disease–related brain changes in MRI: white matter lesions ranging from punctate foci (upper left) to extensive confluent abnormalities (lower left) and lacunar infarcts (lower right).
The Nun Study

- Longitudinal study of aging and Alzheimer's disease
- David Snowden Ph.D. (U. Ky.; U. Minn.)
- Begun in 1986; funded by the National Institute on Aging
- Participants: 678 members of the School Sisters of Notre Dame, now (2009) in their late 70s to > 100 years of age

CVD: Lacunar infarcts
Brain infarction and the clinical expression of Alzheimer disease: The Nun Study

David A. Snowdon PhD et al JAMA (1997)

Among 61 participants who met neuropathologic criteria for AD, those with brain infarcts had poorer cognitive function and a higher prevalence of dementia than those without infarcts. Participants with lacunar infarcts in the basal ganglia, thalamus, or deep white matter had an especially high prevalence of dementia, compared to those without infarcts (OR = 20.7). Fewer neuropath lesions of AD appeared to result in dementia in those with lacunar infarcts in the basal ganglia, thalamus, or deep white matter, than in those without infarcts. In contrast, among 41 participants who did not meet neuropath criteria for AD, brain infarcts were only weakly associated with poor cognitive function and dementia. Among all 102 participants, atherosclerosis of the circle of Willis was strongly associated with lacunar and large brain infarcts.

These findings suggest that cerebrovascular disease may play an important role in determining the presence and severity of the clinical symptoms of AD.

Potentially Controllable CVD Risk Factors

- Cigarette smoking
- Poor nutrition
- Physical inactivity
- Excessive alcohol use
- HTN
- Hypercholesterolemia
- Diabetes
- Syndrome X (aka Metabolic s.; Insulin resistance s.)
- Atherosclerosis →
- Impaired cerebral blood flow →
- Brain infarction
Diet and Nutrition

- Saturated fats/transfats/cholesterol
  - ↑ serum cholesterol
  - ↑ atherosclerosis and CVD
  - Unsaturated fats protective (omega-3)

- Homocysteine
  - High level associated with ↑ risk of CV events
  - ↑ Risk of AD via potentiation of copper and Aβ peptide neurotoxicity
  - Can be caused by deficiency in folic acid, B6, B12
  - Although evidence for the benefit of lowering Hcy is lacking, patients at ↑ risk should be advised to get enough folic acid and B vitamins in their diet

Walter Willett
In the ageing process, neural areas and cognitive processes do not degrade uniformly. Executive control processes and the prefrontal and frontal brain regions that support them show large and disproportionate changes with age. Studies of adult animals indicate that metabolic and neurochemical functions improve with aerobic fitness. We therefore investigated whether greater aerobic fitness in adults would result in selective improvements in executive control processes, such as planning, scheduling, inhibition and working memory. Over a period of six months, we studied 124 previously sedentary adults, 60 to 75 years old, who were randomly assigned to either aerobic (walking) or anaerobic (stretching and toning) exercise. We found that those who received aerobic training showed substantial improvements in performance on tasks requiring executive control compared with anaerobically trained subjects.
Cardiovascular Fitness, Exercise and Memory: The heart-brain connection

- **Effects of exercise**
  - ↑ Lung function
  - ↑ Cerebral blood flow
  - ↓ CVD risk factors (HTN, hypercholesterolemia, obesity)

- **CV health augments brain plasticity**
  - ↑ Capillary growth around neurons
  - ↑ Synaptic density
  - ↑ Positive cholinergic effects
  - ↑ NGF for neuronal maintenance and repair

2007 Exercise guidelines for health adults under age 65
American College of Sports Medicine/American Heart Association

- Moderately intense cardio 30 minutes a day, 5 days a week
- Or
- Vigorously intense cardio 20 minutes a day, 3 days a week
- And
- 8 to 10 strength-training exercises, 8 to 12 repetitions of each exercise twice a week.

Moderate-intensity physical activity means working hard enough to raise your heart rate and break a sweat, yet still being able to carry on a conversation.

The 30-minute recommendation is for the average healthy adult to maintain health and reduce the risk for chronic disease.

To lose weight or maintain weight loss, 60 to 90 minutes of physical activity may be necessary.
Your Brain: Use It or Lose It

- MacArthur Foundation study
  - Years of education correlates most robustly with cognitive outcome in aging
- High levels of education convey neuroprotective effect in withstanding AD pathology
- Rush U study: frequency of engagement in intellectually stimulating activity better predicts dementia diagnosis than years of education
- Importance of Lifelong Learning

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Social Involvement and Memory

- MacArthur study: social support ↑ cognitive function
- Canadian study (2003): ↓ social engagement predicted cognitive decline
- May ↑ likelihood of involvement in intellectually stimulating activities AND help down-regulate or more effectively manage emotional stress

Sleep

- Restoration for optimal alertness and focus
- Memory consolidation
- Sleep disordered breathing (OSA)
  - Fragmentation of sleep architecture
  - Degradation of consolidation
Alcohol

- Excessive use is neurotoxic
- Korsakoff’s syndrome (thiamine deficiency)
- Moderate use may be protective

- Prospective population-based study of almost 7983 people, 55+
- Controlled for age, gender, education, BP, BMI
- Light-Moderate use associated with reduced risk of all types of dementia

Mechanism?
- Stimulates release of acetylcholine in hippocampus?
- ↓ CV risk by altering lipid metabolism?

Stress and the Hypothalamic-Pituitary-Adrenal Axis
The General Adaptation Syndrome

- Sensory info processed by amygdala – Fear Response
- Activation of hypothalamus
- Hypothalamus activates sympathetic NS and HPA, secretes CRH
- CRH stimulates pituitary to produce ACTH
- ACTH stimulates release of glucocorticoids (cortisol) from adrenal gland
- ↑ Levels can damage MTL via hippocampal atrophy
T1-weighted MRI: extensive hippocampal atrophy

Feldman, H. H. et al. CMAJ 2008;178:825-836

Proton MRS of the hippocampus and occipital white matter in PTSD

Villareal et al, Canadian J of Psychiatry, 2002

- Assessed neurometabolite concentrations
- Trend toward ↓ hipp. NAA and creatine in PTSD
- ↓ hipp neuronal integrity
Genetic influences on memory

- **AD genes**
  - ApoE (Apolipoprotein E) – allele 4
  - PS-1, PS-2 (Presenilin) mutations
  - APP (amyloid precursor protein) mutations can dramatically ↑ Aβ production

- **Brain derived nerve growth factor (BDNF)**
  - Directs production of NGF
    - Met variant: ↓ episodic memory
    - Val variant: ↑ episodic memory
    - Differing patterns of hippocampal activation

Seven Commandments for Optimal Brain Aging

1. Thou shalt chose thy parents wisely
2. Thou shalt minimize risk factors for cerebrovascular disease (HTN, Hyperlipidemia, DM)
   - Nutrition – see Walter Willett's Healthy Eating Pyramid
   - Exercise – healthy adults 18-65: moderate aerobic activity minimum 30 minutes 5 days/week or vigorous aerobic activity minimum 20 minutes 3 days/week
3. Thou shalt maintain intellectual engagement throughout life
4. Thou shalt cultivate and sustain friendship and good company
5. Thou shalt obtain restful and restorative sleep
6. Thou shalt enjoy alcohol in moderation
7. Thou shalt manage stress effectively
Cognitive Enhancers
The quest for a smart pill

Brain power over the Internet:
No prescription needed

- www.ironpower.biz/pharmacy_buy_provigil_online
- www.buy-adderall.com/
- www.trustedonlinepharmacy.com/buy-ritalin
- www.drugdelivery.ca/s358-s-ARICEPT
Cosmetic Neurology:
The controversy over enhancing movement, mentation, and mood.

NEUROLOGY
2004, 968-974

Cognitive Enhancement

- Rose SPR. “Smart drugs”: do they work? Are they ethical? Will they be legal?. Nature Reviews Neuroscience, 2002
Where the women are strong, the men are good-looking, and all the children are above average.