Neural Development 2

https://www.alz.org/
Symptoms

- Memory loss that disrupts daily life
- Challenges in planning or solving problems
- Difficulty completing familiar tasks at home, at work or at leisure
- Confusion with time or place
- Trouble understanding visual images and spatial relationships
- New problems with words in speaking or writing
- Misplacing things and losing the ability to retrace steps
- Decreased or poor judgment
- Withdrawal from work or social activities
- Changes in mood and personality

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Alzheimer’s disease (AD)

• In Canada
  – 2015: ~750,000 have AD or related dementia
  – 2035: ~1.5 million

• About 1 in 10 Canadians over 65 years has AD or a related dementia
Myths about AD

• AD is largely the result of genetics.
• AD is a disease that only affects the elderly.
• There is a cure for AD.
• Memory loss = AD
• Other possible myths? Discuss with your neighbor.
Risk Factors for AD

- Age
- Genetics (ApoE gene, other genes)
- Female gender (following menopause)
- Obesity
- Type 2 Diabetes Mellitus
- Cardiovascular disease
- Few pharmacological treatments
- Can non-pharmacological manipulations help?
mouse model of AD (3xTg-AD mouse)

three mutations associated with familial Alzheimer's disease (APP Swedish, MAPT P301L, and PSEN1 M146V)

amyloid (Aβ) plaques & neurofibrillary (phosphoTau) tangles
• Female mice
• Non-transgenenic (NTg) or transgenic (Tg)
• At 4 months of age (young adults):
  – Sham surgery
  – Ovariectomy (Ov)
• At 6 months of age:
  – No running wheel
  – Running wheel (Ex)
• At 9 months of age:
  – Morris Water Maze etc.
• 3 days after behavior testing, hippocampus and cerebral cortex were collected
• Thus, 8 groups (n=8-9 subjects per group)
Morris Water Maze (Probe Trial)

Figure 4  Effects of ovariectomy and physical exercise on spatial memory acquisition and retention in 3×Tg-AD (Tg) and non-transgenic (NTg) mice measured by the Morris water maze test. (A) Swimming distance to reach the platform location. (B) Time spent swimming in the platform quadrant of the pool and in the opposite quadrant after removal of the platform to test the retention of learning. Ovariectomy partially worsened place task acquisition and impaired memory retention in NTg mice. Exercise ameliorated learning and memory in the ovariectomized NTg mice and all Tg mice. Values are the mean ± SEM, n = 8–9. See text for statistics in (A); *p < 0.05, **p < 0.01, ***p < 0.001 compared to the platform quadrant for each experimental group in (B) (Bonferroni).
Morris Water Maze (Probe Trial)

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Figure 5  Effects of ovariectomy and physical exercise on the amyloid β and tau pathology in cerebral cortical tissue of 3×Tg-AD (Tg) mice. (A) Representative immunoblot and densitometric analysis of the APP carboxy-terminal fragment C99 relative to APP levels (C99/APP). (B) Representative immunoblots and densitometric analyses of p-tau protein detected with clone AT8. Data were normalized to pan actin levels. Ovariectomy did not induce a worsening of amyloid and tau pathology in cerebral cortex. Physical exercise induced a marginal reduction of C99/APP levels. Values are the mean ± SEM, n = 4. *p < 0.05 compared to NonTg (Bonferroni).
Figure 5  Effects of ovariectomy and physical exercise on the amyloid β and tau pathology in cerebral cortical tissue of 3×Tg-AD (Tg) mice. (A) Representative immunoblot and densitometric analysis of the APP carboxy-terminal fragment C99 relative to APP levels (C99/APP). (B) Representative immunoblots and densitometric analyses of p-tau protein detected with clone AT8. Data were normalized to pan actin levels. Ovariectomy did not induce a worsening of amyloid and tau pathology in cerebral cortex. Physical exercise induced a marginal reduction of C99/APP levels. Values are the mean ± SEM, n = 4. *p < 0.05 compared to NonTg (Bonferroni).
• Olga Kotelko (1919-2014)
• Started training for track and field when 77 years old
• 3-hr sessions, 3x per week
• Over 30 world records in her age category
• On various memory and speed tasks, she (93 years old) outperformed 60-78 year-olds (but not young adults)
• Compared to 60-78 year olds, increased white matter integrity – corpus callosum
The Neurobiology of Exercise

Structure
- Cognitive Controls: Hippocampus, Cortex
- Executive Controls: Prefrontal & Cingulate Cortex
- Emotional Controls: Amygdala, Prefrontal Cortex
- Motivational Controls: Reward,Wanting,Selection
- Motor Controls: Motor Cortex, Striatum, Brainstem, Cerebellum, Spinal Cord

CNS
- Repair
- Plasticity
- Protection
- Neurogenesis
- Transcription
- NA, 5-HT, GABA, Glutamate, Glycine
- BDNF/TrkB
- ERK/CREB
- NFkB

Function
- Learning & Memory
- Behavior
  - Social
  - Sexual
  - Coping
  - Addictive
  - Escape
  - Fight & Flight
  - Stress
  - Sleep
  - Ingestive

Disease
- Alzheimer's Dementia
- Schizophrenia
- Depression
- Sleep Disorders
- Obesity
- Diabetes
- CVD
- Immune Disorders
- IBD, Constipation, Colon Cancer

Internal Feedback
- "Consequences of exercise"

External input
- Visual
- Olfactory
- Acoustic
- Gustatory
- Somatosensory

Humoral Factors
- Neural Primary Afferents

"Exercise"

Muscle
- Cardiovascular Consequences
- Metabolic Consequences: Liver, WAT, Pancreas
- Thermal Consequences

Gastrointestinal Control

Energy Balance

ANS & Endocrine systems

Parkinson's Disease
- ROS

DA
Box 5. Outstanding questions

- What are the relevant principles for the timing, duration, sequence, and type of cognitive engagement that interact positively with exercise on micro- and macroscale outcomes that are important for cognitive and brain health?
- Does physical activity have to increase your heart rate to be neuroprotective? Some studies suggest not (e.g., [61,92,297,23]), but other studies show a dose-response relationship between increases in fitness and brain outcomes (e.g., [28,55,124]). The answer to this question is important for informing public health recommendations for improvement and maintenance of brain health throughout the lifespan.
- There is growing evidence that resistance exercise, which is targeted for improved muscle strength, is also beneficial for brain structure and function in older adults [298,299]. The neural mechanisms may be evaluated through the development of animal models of resistance training and then compared with aerobic training.
- What is the time course of exercise-induced changes in the human brain and how does it vary as a function of age, disease, and presence of brain injury? Can a reliable mapping between time course in animals and humans be established?
- Can small-animal imaging be used to examine the cellular and molecular basis of exercise-induced changes in brain structure and function (e.g., resting-state BOLD coupling) as measured via MRI methods comparable with human studies?
- What is the relationship between exercise-induced changes in peripheral growth factors and regional changes in central expression?