Exercise as a Therapy for Cognitive Aging and Alzheimer's Disease

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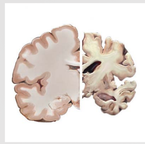
Bass Connections in Brain & Society

Introduction

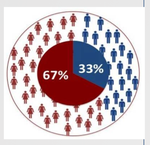
Alzheimer's Disease (AD)

- AD is a progressive, age-related neurodegenerative disease that causes neuronal damage and death and leads to profound memory problems and cognitive impairment
- AD is the 6th leading cause of death in the U.S. and 1/3 of seniors die with AD; AD is the only of the top 10 causes of death that can't be prevented, slowed, or cured

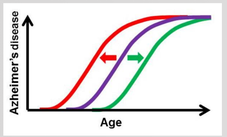


2/3rds of AD Patients are Women

- Women experience greater severity, more neuropathology, earlier onset and faster progression than men do
- Loss of ovarian function during menopause may be a key factor in women's increased risk and accelerated cognitive and neuropathological declines.



Hypothesis and Specific Aims

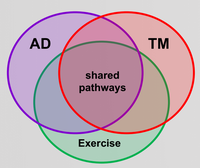


Hypothesis:

1. Menopause exacerbates AD
2. Exercise attenuates AD and its exacerbation by menopause

Specific Aims:

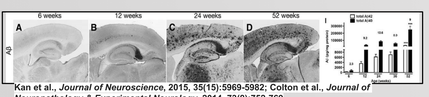
1. Determine the effects of transitional menopause (TM) on memory, neuropathogenesis, and gene expression in female AD and control mice.
2. Determine the effects of exercise experienced during pre-, peri-, and postmenopausal stages on cognitive function, neuropathogenesis and gene expression in AD females.



Creating a mouse model of female physiology in AD

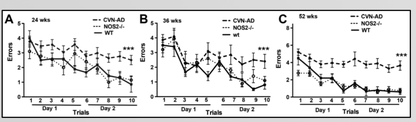
CVN-AD Mouse Model

Timeline for AD-like pathogenesis
Amyloid pathology

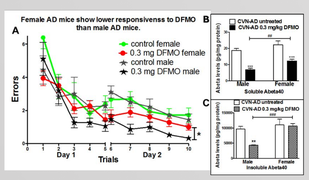


Kan et al., *Journal of Neuroscience*, 2015, 35(15):5969-5982; Colton et al., *Journal of Neuropathology & Experimental Neurology*, 2014, 73(8):752-769

Spatial memory deficits

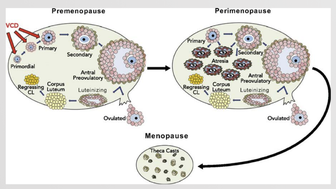


Sex differences in pathogenesis



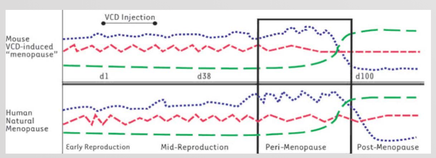
Transitional Menopause (TM) Mouse Model

Accelerated ovarian failure following treatment with the ovotoxin VCD



Brooks et al., *Physiology*, 2016, 31:250-257

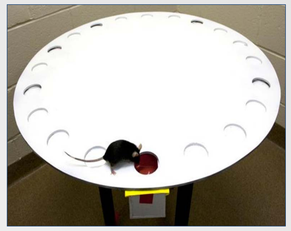
Treatment of mice with VCD results in a transition to menopause that mirrors human menopause



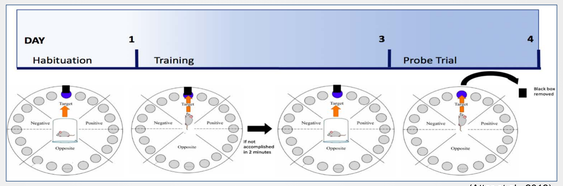
Preliminary Behavioral Testing: Barnes Maze

Overview & Procedures:

- The Barnes Maze was used to evaluate the ability of mice to locate a single escape hole (among 20 holes) that contianed a safe black drawer, and to remember--using spatial cues--this target in a subsequent probe trials.
- White noise and bright lights were used to encourage the mice to escape, and were promptly turned off once the mice successfully escaped into the hole.
- To reduce locational preferences due to external factors, the mice were evenly divided to train to targets in directly opposite quadrants from each other



Barnes maze habituation, training, and the probe trial demonstration

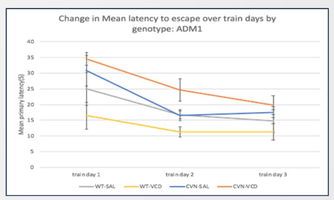


(Attar et al., 2013)

Results:

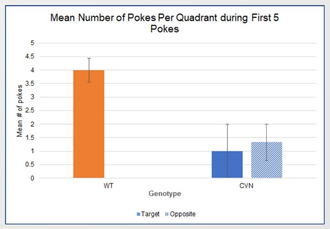
TM makes AD mice learn slower than their saline counterparts:

At 14 months of age, AD-VCD had a slower mean latency to the target location than their saline counterparts. However, the opposite occurred in the WT mice. This suggests AD-VCD mice experience TM-induced cognitive deficits, while WT do not.

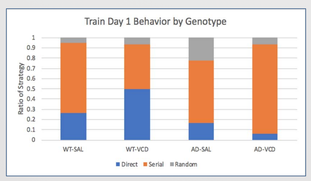


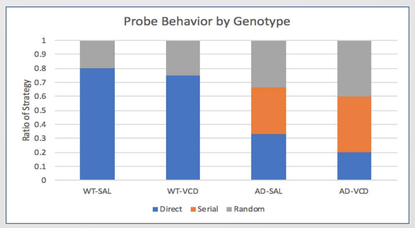
AD mice show poor memory for target location in a Barnes Maze task:

During the first five nose pokes of a Barnes Maze probe trial, WT mice explored the target quadrant, while AD mice struggled to differentiate between the target quadrant and the opposite quadrant. This indicates that while the WT mice remember the location of the escape, the AD mice do not.



AD mice use a learned strategy rather than a hippocampal-dependent strategy in a Barnes Maze task:





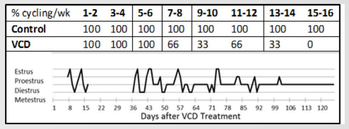
During day 1 of training, all genotypes preferred a serial strategy of exploring consecutive holes until the target hole. By the probe trial, wild type mice had shifted to a direct approach of going directly to the target hole, while the AD mice continued to prefer a serial or random strategy. This shift indicates that while the wild type eventually used hippocampal dependent memory, AD mice only used a learned strategy.

Methodology

- VCD--a toxin that kills ovarian follicles to initiate transitional menopause--or saline will be administered to AD or control mice and daily vaginal smears will monitor cycles.
- AD females will then be subjected to exercise training at 3 time periods corresponding to 3 stages of typical AD cognitive decline and neuropathogenesis.
- Exercise training will include daily voluntary wheel running of 6 hours/day and forced treadmill running for 1 hour, 3 days/week, thus mimicking an active lifestyle and weekly "visits to the gym."

VCD Timeline

% cycling/wk	1-2	3-4	5-6	7-8	9-10	11-12	13-14	15-16
Control	100	100	100	100	100	100	100	100
VCD	100	100	100	66	33	66	33	0



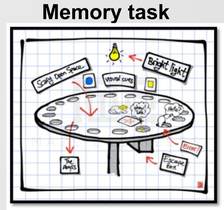
Over the course of about 16 weeks, mice injected with ovotoxin VCD cease to cycle between menstrual phases, thus reaching a state comparable to menopause.

Treatment Training

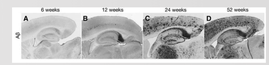
Voluntary Wheel Running

Outcome Measures

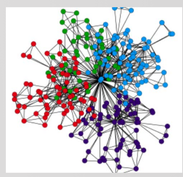
1. Cognitive Assessment: Memory task



2. Brain Pathology



3. Brain Pathways and Networks

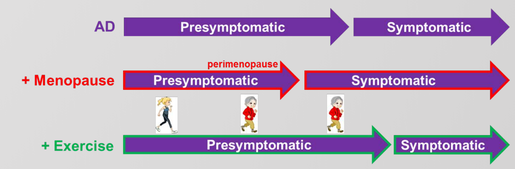


Summary and Potential Outcomes

- So far, our first hypothesis that TM worsens AD has been partially supported. Our second hypothesis on exercise and AD will be tested this coming summer

These studies will:

- Provide a proof-of-principle test for our hypothesis that menopause exacerbates and exercise attenuates AD pathogenesis
- Create a foundational framework for more comprehensive and mechanistic future investigation on the impact of interactions among AD, menopause, aging, and exercise on female brain health



Future Directions:

- To investigate underlying mechanisms using proteomic, metabolomic, and other approaches
- To compare different types and timing of exercise interventions
- To investigate menopause and exercise effects in other mouse models of AD and neurodegenerative diseases

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